For John Dantzman.

U.S. DEPARTMENT OF COMMERCE
Patent and Trademark Office

SEARCH REQUEST FORM

2-76

Requestor's Name: B Celsa

Serial Number: 08/874,992

Date: 2/1/99

Phone: 305-7556

Art Unit: 1654

9A09

Search Topic:
Please write a detailed statement of search topic. Describe specifically as possible the subject matter to be searched. Define any terms that may have a special meaning. Give examples or relevent citations, authors, keywords, etc., if known. For sequences, please attach a copy of the sequence. You may include a copy of the broadest and/or most relevent claim(s).

Use of nitrosated (NO, SNO) or nitrosylated Hemoglobins (e.g. SNO-Hb (Fe II)O_2 or NO-Hb (Fe II)) for treating platelet-related disorders.

Please

1) search elected claims 15-17 in relevant databases (STN, dialog etc)
2. Please - search inventors
3. can combine 1 & 2
4. any other search deemed relevant

tx

Bennett

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Date completed: 2-5-99	**Search Site**	**Vendors**
Searcher: JOHN DANTMAN	___ STIC	✓ IG
Terminal time: ___	✓ CM-1	___ STN
Elapsed time: ___	___ Pre-S	___ Dialog
CPU time: ___	**Type of Search**	___ APS
Total time: ___	___ N.A. Sequence	___ Geninfo
Number of Searches: ___	___ A.A. Sequence	___ SDC
Number of Databases: ___	___ Structure	___ DARC/Questel
	___ Bibliographic	___ Other

PTO-1590 (9-90)

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=>  D HIS

     (FILE 'HOME' ENTERED AT 13:02:29 ON 05 FEB 1999)

     FILE 'HCAPLUS' ENTERED AT 13:02:38 ON 05 FEB 1999
L1          227 S STAMLER J?/AU
L2           78 S GOW A?/AU
L3            3 S L1 AND L2
L4          302 S (L1 OR L2)
L5           41 S L4 AND (PLATELET? OR MYOCARD? OR THROMB? OR SEPSIS OR
ANGIN?)
L6       162157 S (PLATELET? OR MYOCARD? OR THROMB? OR SEPSIS OR ANGIN?)
L7          193 S L6 AND (SNO OR NO OR NITROSYLAT? OR NITROSAT?)(6A)(HB OR
HEMO
L8            6 S L7 AND L5
L9            8 S L3 OR L8
                SELECT RN L9 1-8

     FILE 'REGISTRY' ENTERED AT 13:06:10 ON 05 FEB 1999
L10          46 S E1-46

     FILE 'HCAPLUS' ENTERED AT 13:06:24 ON 05 FEB 1999
L11           7 S L9 AND L10
L12           1 S L9 NOT L11

     FILE 'BIOSIS, MEDLINE, EMBASE, WPIDS' ENTERED AT 13:09:10 ON 05 FEB 1999
L13           9 S  L3
L14           6 S L8
L15          14 S L13 OR L14
L16           8 DUP REMOV L15 (6 DUPLICATES REMOVED)

     FILE 'HCAPLUS' ENTERED AT 13:12:39 ON 05 FEB 1999
L17         120 S L6(20A)(SNO OR NO OR NITROSYLAT? OR NITROSAT?)(6A)(HB OR
HEMO
L18          12 S L17 AND NITRO?
L19           9 S L18 NOT L9
L20           0 S L17 AND (SNO OR NO)(2W)(HB OR HEMOGLOBIN)(2A)(FE2 OR FEII
OR
L21           0 S L6 AND (SNO OR NO)(2W)(HB OR HEMOGLOBIN)(2A)(FE2 OR FEII OR
F

     FILE 'ADISALERTS, ADISINSIGHT, AIDSLINE, BIOSIS, CANCERLIT, CAPLUS, CEN,
     DGENE, DRUGB, DRUGLAUNCH, DRUGMONOG2, DRUGNL, DRUGU, EMBAL, EMBASE,
     IFIPAT, IPA, JICST-EPLUS, KOSMET, LIFESCI, MEDLINE, NAPRALERT, NLDB,
     PHIC, PHIN, SCISEARCH, TOXLINE, TOXLIT, ...' ENTERED AT 13:18:29 ON 05
     FEB 1999

     FILE 'HCAPLUS' ENTERED AT 13:56:54 ON 05 FEB 1999
L22           8 S L6 AND NO HEMOGLOB?
L23          16 S L6 AND NO(1W)HEMOGLOB?
L24          11 S L6 AND (SNO OR NITROS?)(2W)(HB OR HEMOGLOB? OR HAEMOGLOB?)
L25           3 S L6 AND (NITROSOHB OR NITROSYLHAEM?)
L26          26 S L22-L25
L27          21 S L26 NOT (L9 OR L11)

     FILE 'MEDLINE, BIOSIS, CEN, DRUGB, DRUGLAUNCH, DRUGMONOG2, DRUGNL,
DRUGU,
     EMBAL, EMBASE, JICST-EPLUS, LIFESCI, NLDB, PHIC, PHIN, SCISEARCH'
ENTERED
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     AT 14:03:17 ON 05 FEB 1999
L28       1815111 S (PLATELET? OR MYOCARD? OR THROMB? OR SEPSIS OR ANGIN?)
L29            10 S L28 AND (SNO OR NITROSYLAT? OR  NITROSAT?)(6A)(HB OR
HEMOGLOB
L30             0 S L28 AND (NITROSOHB OR NITROSYLHAEM?)
L31            69 S L28 AND NO(1W)(HB OR HAEMOGLOB? OR HEMOGLOB?)
L32            38 S  L31 AND NITRIC OXIDE
L33            48 S L29 OR L32
L34             4 DUP REMOV L29 (6 DUPLICATES REMOVED)
L35            20 DUP REMOV L32 (18 DUPLICATES REMOVED)
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=> d his

     (FILE 'HOME' ENTERED AT 13:02:29 ON 05 FEB 1999)

     FILE 'HCAPLUS' ENTERED AT 13:02:38 ON 05 FEB 1999
L1          227 S STAMLER J?/AU
L2           78 S GOW A?/AU
L3            3 S L1 AND L2
L4          302 S (L1 OR L2)
L5           41 S L4 AND (PLATELET? OR MYOCARD? OR THROMB? OR SEPSIS OR
ANGIN?)
L6       162157 S (PLATELET? OR MYOCARD? OR THROMB? OR SEPSIS OR ANGIN?)
L7          193 S L6 AND (SNO OR NO OR NITROSYLAT? OR NITROSAT?)(6A)(HB OR
HEMO
L8            6 S L7 AND L5
L9            8 S L3 OR L8
                SELECT RN L9 1-8

     FILE 'REGISTRY' ENTERED AT 13:06:10 ON 05 FEB 1999
L10          46 S E1-46

     FILE 'HCAPLUS' ENTERED AT 13:06:24 ON 05 FEB 1999
L11           7 S L9 AND L10
L12           1 S L9 NOT L11
```

INVENTOR SEARCH

=> d all

L12 ANSWER 1 OF 1 HCAPLUS
AN 1998:765570 HCAPLUS
TI Nitrosative stress: metabolic pathway involving the flavohemoglobin
AU Hausladen, Alfred; **Gow, Andrew J.; Stamler, Jonathan S.**
CS Department of Medicine, Duke University Medical Center, Durham, NC, 27710, USA
SO Proc. Natl. Acad. Sci. U. S. A. (1998), 95(24), 14100-14105
CODEN: PNASA6; ISSN: 0027-8424
PB National Academy of Sciences
DT Journal
LA English
CC 6 (General Biochemistry)
AB Nitric oxide (NO) biol. has focused on the tightly regulated enzymic mechanism that transforms L-arginine into a family of mols., which serve both signaling and defense functions. However, very little is known of the pathways that metabolize these mols. or turn off the signals. The paradigm is well exemplified in bacteria where S-nitrosothiols (SNO)-compds. identified with antimicrobial activities of NO synthase-elicit responses that mediate bacterial resistance by unknown mechanisms. Here we show that Escherichia coli possess both constitutive and inducible elements for SNO metab. Constitutive enzyme(s) cleave SNO to NO whereas bacterial Hb, a widely distributed flavoHb of poorly understood function, is central to the inducible response. Remarkably, the protein has evolved a novel heme-detoxification mechanism for NO. Specifically, the heme serves a dioxygenase function that produces mainly nitrate. These studies thus provide new insights into SNO and NO metab. and identify enzymes with reactions that were thought to occur only by chem. means. Our results also emphasize that the reactions of SNO and NO with Hbs are evolutionary conserved, but have been adapted for cell-specific function.

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=> d l11 bib abs hitstr

L11  ANSWER 1 OF 7  HCAPLUS  COPYRIGHT 1999 ACS
AN   1998:550442  HCAPLUS
DN   129:172133
TI   NO-modified hemoglobins, therapeutic uses therefor,
     and methods for determination of NO in NO-
     hemoglobin
IN   Stamler, Jonathan S.; Gow, Andrew J.
PA   Duke University Medical Center, USA
SO   PCT Int. Appl., 167 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 1
     PATENT NO.       KIND  DATE          APPLICATION NO.  DATE
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PI   WO 9834955        A1   19980813      WO 98-US2383     19980205
         W:  AU, CA, JP, US
         RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT,
SE
     AU 9861502        A1   19980826      AU 98-61502      19980205
PRAI US 97-796164      19970206
     US 97-874992      19970612
     WO 98-US2383      19980205
AB   S-nitrosoHb (SNO-Hb) can be formed by reaction of Hb
     with S-nitrosothiol and by other methods described herein which do not
     result in oxidn. of the heme Fe.  Other methods can be used which are not
     specific only for thiol groups, but which nitrosate Hb
     more extensively, and may produce polynitrosated metHb as a product or
     intermediate product of the method.  SNO-Hb in its
     various forms and combinations thereof (oxy, deoxy, met; specifically
     S-nitrosylated, or nitrosated or nitrated to various extents) can be
     administered to an animal or human where it is desired to oxygenate, to
     scavenge free radicals, or to release NO+ groups to tissues.  Thiols
     and/or NO donating agents can also be administered to enhance the
transfer
     of NO+ groups.  Examples of conditions to be treated by SNO-
     Hbs or other nitrosated or nitrated forms of Hb
     include ischemic injury, hypertension, angina, reperfusion
     injury and inflammation, and disorders characterized by thrombosis
     .  Further embodiments of the invention are methods for assessing oxygen
     delivery to the tissues of a mammal by measuring SNO-Hb
     and nitrosylHb in blood.  The reaction of NO with Hb
     in blood and erythrocytes, the effects of various physiol. conditions on
     these reactions, the physiol. effects of NO-Hb, and
     the therapeutic use of nitrosyl-Hb are presented.
IT   10102-43-9, Nitric oxide, biological studies
     RL: ANT (Analyte); BOC (Biological occurrence); BPR (Biological process);
     THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study);
     OCCU (Occurrence); PROC (Process); USES (Uses)
        (NO-modified Hbs, therapeutic uses therefor, and
        methods for detn. of NO in NO-Hb)
RN   10102-43-9  HCAPLUS
CN   Nitrogen oxide (NO) (8CI, 9CI)  (CA INDEX NAME)
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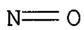
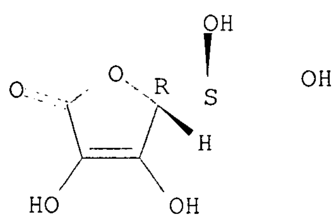


IT **50-81-7DP**, Ascorbic acid, conjugates, with nitrosyl-**Hb**
53-59-8DP, NADP, conjugates, with nitrosyl-**Hb**
53-84-9DP, NAD, conjugates, with nitrosyl-**Hb**
146-14-5DP, FAD, conjugates, with nitrosyl-**Hb**
146-17-8DP, FMN, conjugates, with nitrosyl-**Hb**
490-83-5DP, Dehydroascorbic acid, conjugates, with nitrosyl-**Hb** **9054-89-1DP**, Superoxide dismutase, conjugates, with nitrosyl-**Hb** **13408-29-2DP**, Nitroxide radical, conjugates, with nitrosyl-**Hb** **125978-95-2DP**, Nitric oxide synthetase, conjugates, with nitrosyl-**Hb**
RL: BPR (Biological process); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(**NO**-modified **Hbs**, therapeutic uses therefor, and methods for detn. of **NO** in **NO-Hb**)

RN 50-81-7 HCAPLUS
CN L-Ascorbic acid (8CI, 9CI) (CA INDEX NAME)

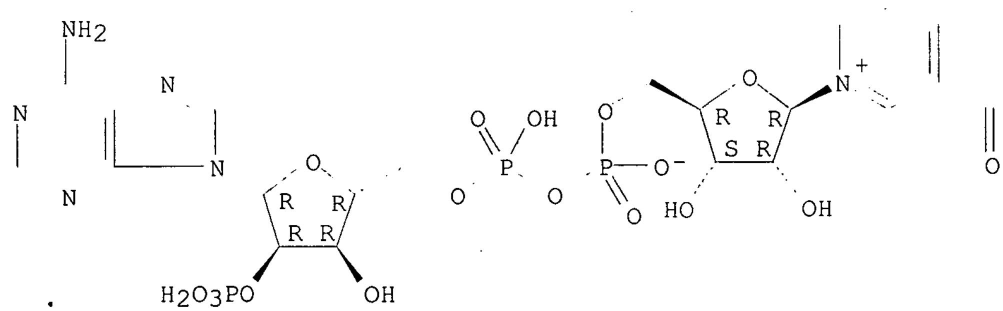
Absolute stereochemistry.



RN 53-59-8 HCAPLUS
CN Adenosine 5'-(trihydrogen diphosphate), 2'-(dihydrogen phosphate), P'.fwdarw.5'-ester with 3-(aminocarbonyl)-1-.beta.-D-ribofuranosylpyridinium, inner salt (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A

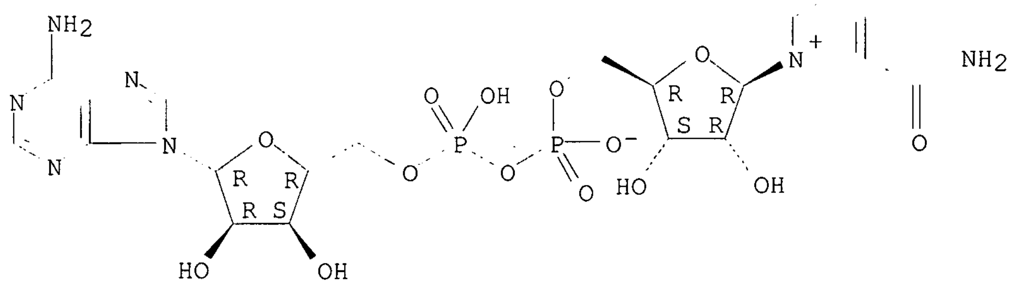


PAGE 1-B

NH2

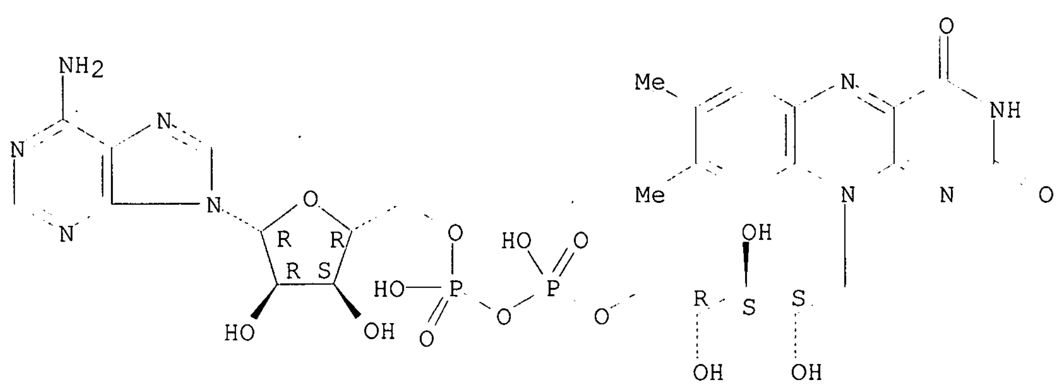
RN 53-84-9 HCAPLUS
CN Adenosine 5'-(trihydrogen diphosphate), P'.fwdarw.5'-ester with 3-(aminocarbonyl)-1-.beta.-D-ribofuranosylpyridinium, inner salt (9CI) (CA INDEX NAME)

Absolute stereochemistry.



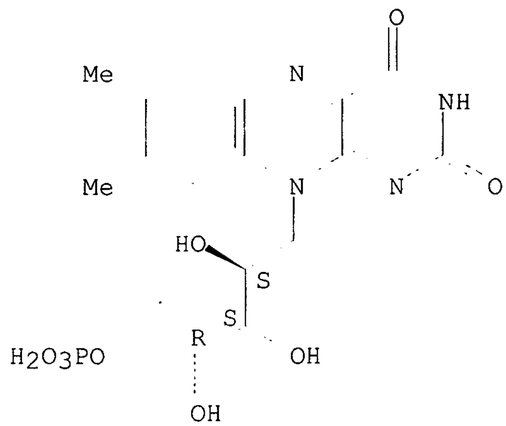
RN 146-14-5 HCAPLUS
CN Riboflavin 5'-(trihydrogen diphosphate), P'.fwdarw.5'-ester with adenosine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



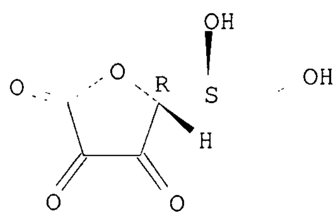
RN 146-17-8 HCAPLUS
CN Riboflavin 5'-(dihydrogen phosphate) (8CI, 9CI) (CA INDEX NAME)

Absolute stereochemistry.



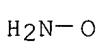
RN 490-83-5 HCAPLUS
CN L-threo-2,3-Hexodiulosonic acid, .gamma.-lactone (9CI) (CA INDEX NAME)

Absolute stereochemistry.



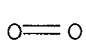
RN 9054-89-1 HCAPLUS
CN Dismutase, superoxide (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 13408-29-2 HCAPLUS
CN Nitroxide (7CI, 8CI, 9CI) (CA INDEX NAME)



RN 125978-95-2 HCAPLUS
CN Synthase, nitric oxide (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT **7782-44-7**, Oxygen, analysis
RL: ANT (Analyte); ANST (Analytical study)
(delivery to body of, assay for; **NO**-modified **Hbs**, therapeutic uses therefor, and methods for detn. of **NO** in **NO-Hb**)
RN 7782-44-7 HCAPLUS
CN Oxygen (8CI, 9CI) (CA INDEX NAME)



IT **10028-15-6**, Ozone, uses
RL: ARG (Analytical reagent use); ANST (Analytical study); USES (Uses)
(in **NO** of **NO-Hb** detn.; **NO**
-modified **Hbs**, therapeutic uses therefor, and methods for
detn. of **NO** in **NO-Hb**)
RN 10028-15-6 HCAPLUS
CN Ozone (8CI, 9CI) (CA INDEX NAME)

O—O—O

IT **55-63-0**, Nitroglycerin **15078-28-1**, Nitroprusside
51209-75-7, S-Nitrosocysteine **57564-91-7**,
S-Nitrosoglutathione **139427-42-2**, S-Nitrosohomocysteine
162758-33-0, S-Nitrosocysteinylglycine
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(in prepn. of **NO-Hb**; **NO**-modified
Hbs, therapeutic uses therefor, and methods for detn. of
NO in **NO-Hb**)
RN 55-63-0 HCAPLUS
CN 1,2,3-Propanetriol, trinitrate (9CI) (CA INDEX NAME)

```
              O— NO2
              |
O2N— O— CH2— CH— CH2— O— NO2
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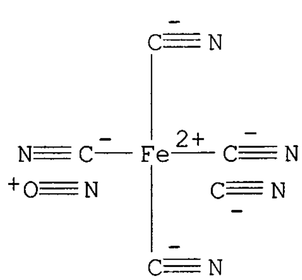
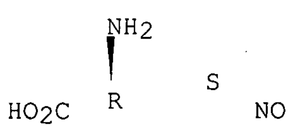
RN 15078-28-1 HCAPLUS
CN Ferrate(2-), pentakis(cyano-.kappa.C)nitrosyl-, (OC-6-22)- (9CI) (CA INDEX NAME)



RN 51209-75-7 HCAPLUS
CN L-Cysteine, nitrite (ester) (9CI) (CA INDEX NAME)

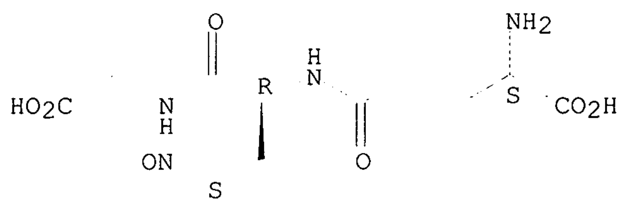
Absolute stereochemistry.



RN 57564-91-7 HCAPLUS

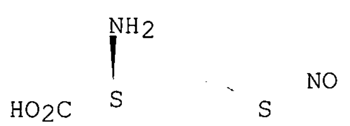
CN Glycine, L-.gamma.-glutamyl-S-nitroso-L-cysteinyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



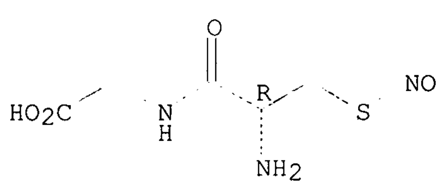
RN 139427-42-2 HCAPLUS
CN L-Homocysteine, nitrite (ester) (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 162758-33-0 HCAPLUS
CN Glycine, S-nitroso-L-cysteinyl- (9CI) (CA INDEX NAME)

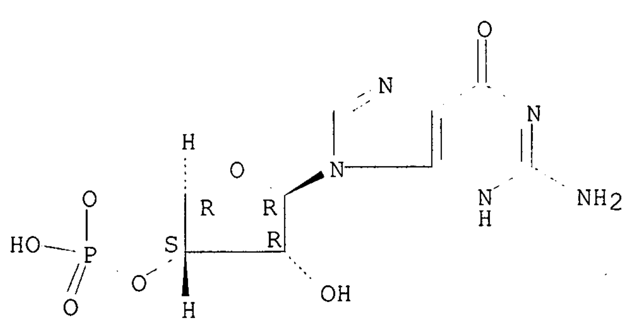
Absolute stereochemistry.



=> d l11 bib abs hitstr 2

L11 ANSWER 2 OF 7 HCAPLUS
AN 1998:90483 HCAPLUS
DN 128:203451
TI Cell-free and erythrocytic S-nitrosohemoglobin inhibits human **platelet** aggregation
AU Pawloski, John R.; Swaminathan, Rajesh V.; **Stamler, Jonathan S.**
CS Howard Hughes Medical Institute, Duke University Medical Center, Durham, NC, 27710, USA
SO Circulation (1998), 97(3), 263-267
CODEN: CIRCAZ; ISSN: 0009-7322
PB Williams & Wilkins
DT Journal
LA English
AB Nitric oxide (NO) and related mols. are thought to inhibit human **platelet** aggregation by raising levels of cGMP. Both oxidative stress (reactive oxygen species) and **Hb** (**Hb**) seem to oppose **NO** effects. A major fraction of NO in the blood is bound to thiols of **Hb**, forming S-nitrosoHb (**SNO-Hb**), which releases the **NO** group on deoxygenation in the microcirculation. Here the authors show that (1) both cell-free and intraerythrocytic **SNO-Hb** (**SNO**-RBC) inhibit **platelet** aggregation, (2) the oxidn. state of the hemes in **Hb** influences the response-**SNO**-metHb (which is functionally similar to SNO-deoxyHb) has greater **platelet** inhibitory effects than SNO-oxyHb, and (3) the mechanism of **platelet** inhibition by **SNO-Hb** is cGMP independent. The authors suggest that the RBC has evolved a means to counteract **platelet** activation in small vessels and the proaggregatory effects of oxidative stress by forming **SNO-Hb**.
IT **7665-99-8**, CGMP
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(cell-free and erythrocytic S-nitrosoHb inhibition of human **platelet** aggregation)
RN 7665-99-8 HCAPLUS
CN Guanosine, cyclic 3',5'-(hydrogen phosphate) (8CI, 9CI) (CA INDEX NAME)

Absolute stereochemistry.



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L11 ANSWER 3 OF 7 HCAPLUS COPYRIGHT 1999 ACS
AN 1998:62180 HCAPLUS
DN 128:227526
TI Reactions between nitric oxide and hemoglobin under physiological conditions
AU **Gow, Andrew J.; Stamler, Jonathan S.**
CS Howard Hughes Med. Inst., Departments of Med. and Cell Biol., Duke Univ. Med. Cent., Durham, NC, 27710, USA
SO Nature (London) (1998), 391(6663), 169-173
CODEN: NATUAS; ISSN: 0028-0836
PB Macmillan Magazines
DT Journal
LA English
AB The tenet of high-affinity nitric oxide (NO) binding to a Hb has shaped the view of heme proteins and of small diffusible signaling mols. Specifically, NO binds rapidly to heme iron in Hb (k .apprxeq. 107 M-1 s-1) and once bound, the NO activity is largely irretrievable (Kd .apprxeq. 10-5 s-1); the binding is purportedly so tight as to be unaffected by O2 or CO. However, these general principles do not consider the allosteric state of Hb or the nature of the allosteric effector, and they mostly derive from the functional behavior of fully nitrosylated Hb, whereas Hb is only partially nitrosylated in vivo. Oxygen drives the conversion of nitrosylHb in the 'tense' T (or partially nitrosylated, deoxy) structure to S-nitrosoHb in the 'relaxed' R (or ligand-bound, oxy) structure. In the absence of oxygen, nitroxyl anion (NO-) is liberated in a reaction producing metHb. The yields of both S-nitrosoHb and metHb are dependent on the NO/Hb ratio. These newly discovered reactions elucidate mechanisms underlying NO function in the respiratory cycle, and provide insight into the etiol. of S-nitrosothiols, metHb and its related valency hybrids. Mechanistic reexamn. of NO interactions with other heme proteins contg. allosteric-site thiols may be warranted.
IT **7782-44-7**, Oxygen, biological studies **10102-43-9**, Nitric oxide, biological studies **14967-78-3**
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(reactions between nitric oxide and Hb under physiol. conditions)
RN 7782-44-7 HCAPLUS
CN Oxygen (8CI, 9CI) (CA INDEX NAME)

O=O

RN 10102-43-9 HCAPLUS
CN Nitrogen oxide (NO) (8CI, 9CI) (CA INDEX NAME)

N=O

RN 14967-78-3 HCAPLUS
CN Nitrate(1-), oxo- (8CI, 9CI) (CA INDEX NAME)

$^{-}N{=}O$

=> d l11 bib abs hitstr 4

L11 ANSWER 4 OF 7 HCAPLUS
AN 1997:302980 HCAPLUS
DN 126:282775
TI Erythrocytes loaded with S-nitrosothiol and uses therefor
IN **Stamler, Jonathan S.**; Bonaventura, Joseph
PA Duke University Medical Center, USA; Stamler, Jonathan S.; Bonaventura, Joseph
SO PCT Int. Appl., 53 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9709972	A1	19970320	WO 96-US14664	19960913
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	RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG				
	CA 2231916	AA	19970320	CA 96-2231916	19960913
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	EP 850053	A1	19980701	EP 96-931551	19960913
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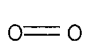
PRAI US 95-3801 19950915
US 96-616255 19960315
WO 96-US14664 19960913

AB Nitric oxide (**NO**) interacts with **Hb** at its metal centers, whereas S-nitrosothiols (RSNOs) can donate the NO group to .beta.93 cysteine residues, thereby shielding the NO functionality from heme inactivation. S-**nitrosylation** of **Hb** is under the allosteric control of oxygen and the oxidn. state of heme. **NO** group release from **SNO-Hb** is further facilitated by intracellular low mol. wt. thiols, forming RSNOs which can be exported from the erythrocyte to regulate blood pressure. Red blood cells can be loaded with low mol. RSNOs to act as a delivery system for NO+ groups. Loaded red blood cells can be used in methods of therapy for conditions which are characterized by abnormal O2 metab. of tissues, oxygen-related toxicity, abnormal vascular tone, abnormal red blood cell adhesion, or abnormal O2 delivery by red blood cells. An example S-nitrosothiols is S-nitrosocysteine.

IT **7782-44-7**, Oxygen, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(delivery; erythrocytes loaded with S-nitrosothiol)
RN 7782-44-7 HCAPLUS
CN Oxygen (8CI, 9CI) (CA INDEX NAME)

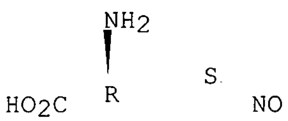


IT **51209-75-7**, S-Nitrosocysteine **139427-42-2**,

S-Nitrosohomocysteine **162758-33-0**
RL: BAC (Biological activity or effector, except adverse); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(erythrocytes loaded with S-nitrosothiol)

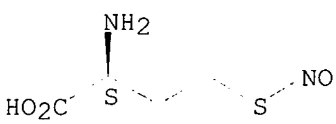
RN 51209-75-7 HCAPLUS
CN L-Cysteine, nitrite (ester) (9CI) (CA INDEX NAME)

Absolute stereochemistry.



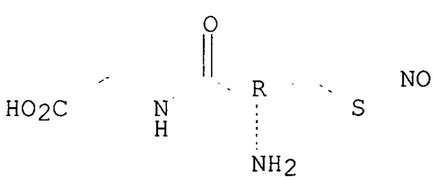
RN 139427-42-2 HCAPLUS
CN L-Homocysteine, nitrite (ester) (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 162758-33-0 HCAPLUS
CN Glycine, S-nitroso-L-cysteinyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **10102-43-9**, Nitric oxide, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(erythrocytes loaded with S-nitrosothiol)

RN 10102-43-9 HCAPLUS
CN Nitrogen oxide (NO) (8CI, 9CI) (CA INDEX NAME)

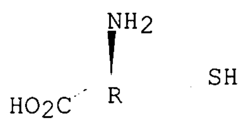
```
=> d l11 bib abs hitstr 5

L11  ANSWER 5 OF 7  HCAPLUS  COPYRIGHT 1999 ACS
AN   1997:284144  HCAPLUS
DN   126:259174
TI   Nitrosated hemoglobins, and their production, for use
     in treatment of ischemic injury, hypertension, angina, and other
     disorders
IN   Stamler, Jonathan S.
PA   Duke University Medical Center, USA; Stamler, Jonathan S.
SO   PCT Int. Appl., 76 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 3
     PATENT NO.       KIND  DATE           APPLICATION NO.  DATE
     ---------------  ----  --------       ---------------  --------
PI   WO 9710265        A1   19970320       WO 96-US14659    19960913
         W:  AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE,
             DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC,
             LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT,
             RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN,
             AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
         RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR,
             IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG
     CA 2232043        AA   19970320       CA 96-2232043    19960913
     AU 9670198        A1   19970401       AU 96-70198      19960913
     EP 850251         A1   19980701       EP 96-931549     19960913
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, FI
PRAI US 95-3801        19950915
     US 96-616371      19960315
     US 96-667003      19960620
     WO 96-US14659     19960913
AB   S-nitrosothiols (RSNOs) can donate the NO group to the .beta.93 cysteine
     residues of Hb (Hb) without inactivating the heme.  S-
     nitrosylation of Hb is under the allosteric control of
     oxygen and the oxidn. state of heme.  NO group release from
     S-nitrosoHb (SNO-Hb) is further facilitated by
     intracellular low mol. wt. thiols, forming RSNOs which can be exported
     from the erythrocyte to regulate blood pressure and platelet
     activation.  SNO-Hb can be formed by reaction of Hb
     with S-nitrosothiol.  This procedure avoids oxidn. of the heme.  Other
     methods can be used which are not specific only for thiol groups, but
     which nitrosate Hb more extensively, and may produce
     polynitrosate metHb as a product or intermediate product of the method.
     SNO-Hb in its various forms and combinations thereof
     (oxy, deoxy, met; specifically S-nitrosylated, or nitrosated or nitrated
     to various extents) can be administered to an animal or human where it is
     desired to oxygenate, to scavenge free radicals, or to release NO+ groups
     to tissues.  Thiols and/or NO donating agents can also be administered to
     enhance the transfer of NO+ groups.  Examples of conditions to be treated
     by SNO-Hbs or other nitrosated or nitrated
     forms of Hb include ischemic injury, hypertension,
     angina, reperfusion injury and inflammation, and disorders
     characterized by thrombosis.
IT   52-90-4, Cysteine, biological studies
```

RL: BOC (Biological occurrence); RCT (Reactant); BIOL (Biological study); OCCU (Occurrence)
(**Hb** Cys residues; **nitrosated Hbs**, and prodn., for use in treatment of ischemic injury, hypertension, **angina**, and other disorders)

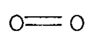
RN 52-90-4 HCAPLUS
CN L-Cysteine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



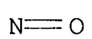
IT **7782-44-7**, Oxygen, biological studies
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(delivery capacity; **nitrosated Hbs**, and prodn., for use in treatment of ischemic injury, hypertension, **angina**, and other disorders, and method for increasing oxygen delivery capacity)

RN 7782-44-7 HCAPLUS
CN Oxygen (8CI, 9CI) (CA INDEX NAME)



IT **10102-43-9**, Nitric oxide, biological studies
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BIOL (Biological study); PROC (Process)
(**nitrosated Hbs**, and prodn., for use in treatment of ischemic injury, hypertension, **angina**, and other disorders)

RN 10102-43-9 HCAPLUS
CN Nitrogen oxide (NO) (8CI, 9CI) (CA INDEX NAME)



IT **9032-80-8**, Methemoglobin reductase
RL: CAT (Catalyst use); USES (Uses)
(**nitrosated Hbs**, and prodn., for use in treatment of ischemic injury, hypertension, **angina**, and other disorders)

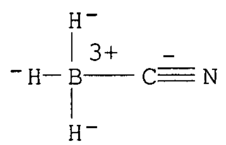
RN 9032-80-8 HCAPLUS
CN Reductase, methemoglobin (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT **33195-00-5**, Cyanoborohydride **51209-75-7**, S-Nitrosocysteine **57564-91-7**, S-Nitrosoglutathione
RL: RCT (Reactant)
(**nitrosated Hbs**, and prodn., for use in treatment of ischemic injury, hypertension, **angina**, and other disorders)

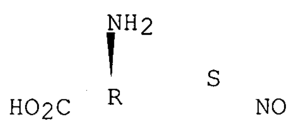
RN 33195-00-5 HCAPLUS

CN Borate(1-), (cyano-.kappa.C)trihydro-, (T-4)- (9CI) (CA INDEX NAME)



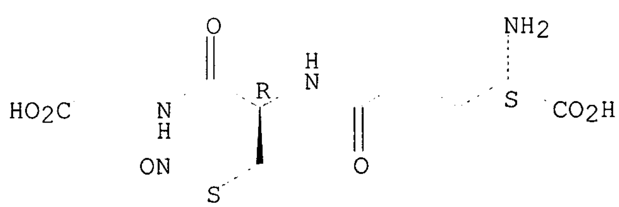
RN 51209-75-7 HCAPLUS
CN L-Cysteine, nitrite (ester) (9CI) (CA INDEX NAME)

Absolute stereochemistry.



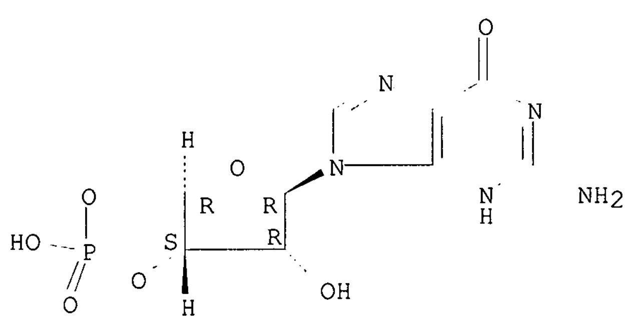
RN 57564-91-7 HCAPLUS
CN Glycine, L-.gamma.-glutamyl-S-nitroso-L-cysteinyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **7665-99-8**, Cyclic GMP
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(**nitrosated Hbs**, and prodn., for use in treatment of ischemic injury, hypertension, **angina**, and other disorders, and effect of nitrosoHbs on cGMP)
RN 7665-99-8 HCAPLUS
CN Guanosine, cyclic 3',5'-(hydrogen phosphate) (8CI, 9CI) (CA INDEX NAME)

Absolute stereochemistry.

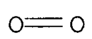


IT **7782-44-7D**, Oxygen, radicals

RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(**nitrosated Hbs**, and prodn., for use in treatment of ischemic injury, hypertension, **angina**, and other disorders, and method for scavenging oxygen free radicals)

RN 7782-44-7 HCAPLUS

CN Oxygen (8CI, 9CI) (CA INDEX NAME)

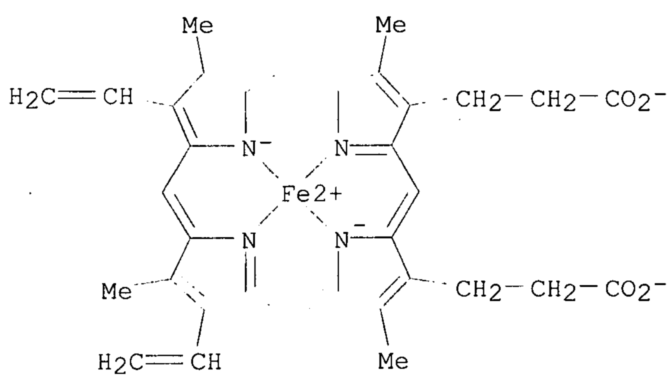


IT **14875-96-8 16009-13-5**

RL: BPR (Biological process); PRP (Properties); BIOL (Biological study); PROC (Process)
(**nitrosated Hbs**, and prodn., for use in treatment of ischemic injury, hypertension, **angina**, and other disorders, and relation to heme iron oxidn. state)

RN 14875-96-8 HCAPLUS

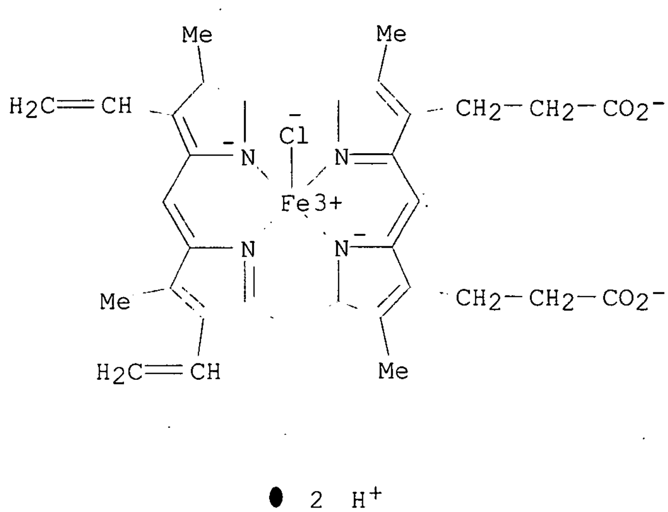
CN Ferrate(2-), [7,12-diethenyl-3,8,13,17-tetramethyl-21H,23H-porphine-2,18-dipropanoato(4-)-.kappa.N21,.kappa.N22,.kappa.N23,.kappa.N24]-, dihydrogen, (SP-4-2)- (9CI) (CA INDEX NAME)



● 2 H^+

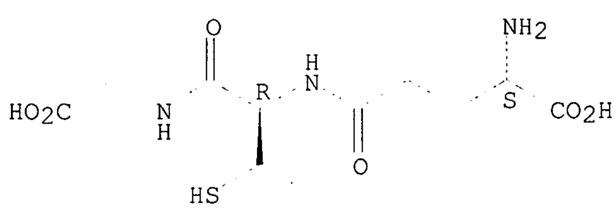
RN 16009-13-5 HCAPLUS

CN Ferrate(2-),
chloro[7,12-diethenyl-3,8,13,17-tetramethyl-21H,23H-porphine-2,18-dipropanoato(4-)-.kappa.N21,.kappa.N22,.kappa.N23,.kappa.N24]-, dihydrogen, (SP-5-13)- (9CI) (CA INDEX NAME)



IT **70-18-8**, Glutathione, biological studies
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(transnitrosation; **nitrosated Hbs**, and prodn., for
use in treatment of ischemic injury, hypertension, **angina**,
and other disorders)
RN 70-18-8 HCAPLUS
CN Glycine, L-.gamma.-glutamyl-L-cysteinyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



=> d l11 bib abs hitstr 6

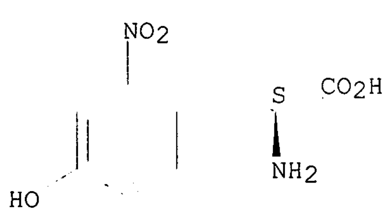
L11 ANSWER 6 OF 7 HCAPLUS
AN 1996:761663 HCAPLUS
DN 126:37023
TI Nitrosylated heme proteins as blood substitutes
IN **Stamler, Jonathan**
PA Brigham and Women's Hospital, USA
SO PCT Int. Appl., 130 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9630006	A1	19961003	WO 96-US3866	19960325
	W: AU, CA, JP				
	RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	AU 9653682	A1	19961016	AU 96-53682	19960325

PRAI US 95-409720 19950324
WO 96-US3866 19960325
AB Blood substitutes comprises a heme protein to which NO or NO2 group is linked directly or indirectly. Tissue plasminogen activator (t-PA) was S-nitrosylated (prepn. given) and **thrombolytic**, anti-**platelet**, and vasodilator effects of S-NO-t-PA were studied.
IT **9047-22-7DP**, Cathepsin b, S-nitroso derivs. **110012-34-5P**
139639-23-9DP, Tissue plasminogen activator, S-nitroso derivs.
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(compns. contg. nitrosylated heme proteins as blood substitutes)
RN 9047-22-7 HCAPLUS
CN Cathepsin B (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 110012-34-5 HCAPLUS
CN L-Tyrosine, 2-nitro- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 139639-23-9 HCAPLUS
CN Plasminogen activator, tissue-type (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT **139639-23-9**, Tissue plasminogen activator
RL: RCT (Reactant)
(compns. contg. nitrosylated heme proteins as blood substitutes)

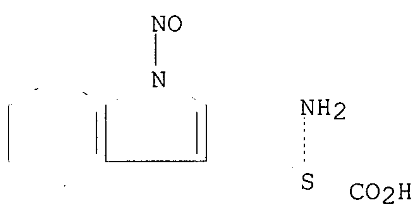
RN 139639-23-9 HCAPLUS
CN Plasminogen activator, tissue-type (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT **949-99-5P 68807-89-6P 183583-02-0P**
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(compns. contg. nitrosylated heme proteins as blood substitutes)
RN 949-99-5 HCAPLUS
CN L-Phenylalanine, 4-nitro- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

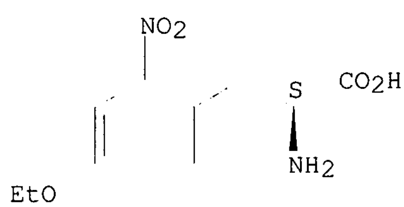
RN 68807-89-6 HCAPLUS
CN L-Tryptophan, 1-nitroso- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

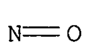


RN 183583-02-0 HCAPLUS
CN L-Tyrosine, O-ethyl-2-nitro- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **10102-43-9**, Nitric oxide, biological studies **10102-43-9D**
, Nitric oxide, compds.
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compns. contg. nitrosylated heme proteins as blood substitutes)
RN 10102-43-9 HCAPLUS
CN Nitrogen oxide (NO) (8CI, 9CI) (CA INDEX NAME)



RN 10102-43-9 HCAPLUS
CN Nitrogen oxide (NO) (8CI, 9CI) (CA INDEX NAME)

N=O

IT **7782-44-7**, Oxygen, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(delivery of; compns. contg. nitrosylated heme proteins as blood substitutes)
RN 7782-44-7 HCAPLUS
CN Oxygen (8CI, 9CI) (CA INDEX NAME)

O=O

IT **463-04-7**, Amyl nitrite **540-80-7**, tert-Butyl nitrite **51209-75-7**, S-Nitroso-cysteine **56577-02-7**, S-Nitroso-N-acetylcysteine **57564-91-7**, S-Nitroso-glutathione **73466-15-6**, S-Nitroso-penicillamine
RL: RCT (Reactant)
(nitrosylation by; compns. contg. nitrosylated heme proteins as blood substitutes)
RN 463-04-7 HCAPLUS
CN Nitrous acid, pentyl ester (8CI, 9CI) (CA INDEX NAME)

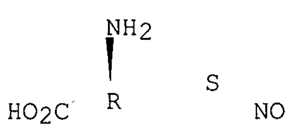
Me—$(CH_2)_4$—O—NO

RN 540-80-7 HCAPLUS
CN Nitrous acid, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

t-Bu—O—NO

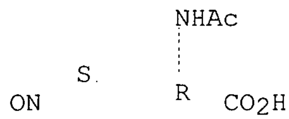
RN 51209-75-7 HCAPLUS
CN L-Cysteine, nitrite (ester) (9CI) (CA INDEX NAME)

Absolute stereochemistry.



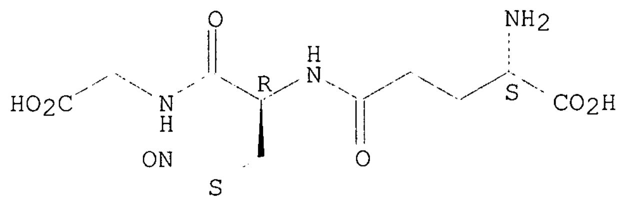
RN 56577-02-7 HCAPLUS
CN L-Cysteine, N-acetyl-S-nitroso- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



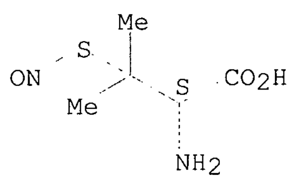
RN 57564-91-7 HCAPLUS
CN Glycine, L-.gamma.-glutamyl-S-nitroso-L-cysteinyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 73466-15-6 HCAPLUS
CN D-Valine, 3-(nitrosothio)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

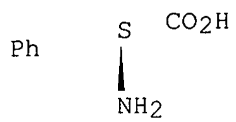


IT **60-18-4**, L-Tyrosine, reactions **63-91-2**, L-Phenylalanine, reactions **73-22-3**, L-Tryptophan, reactions **76757-91-0**
RL: RCT (Reactant)
(nitrosylation of; compns. contg. nitrosylated heme proteins as blood substitutes)
RN 60-18-4 HCAPLUS
CN L-Tyrosine (9CI) (CA INDEX NAME)

Absolute stereochemistry.

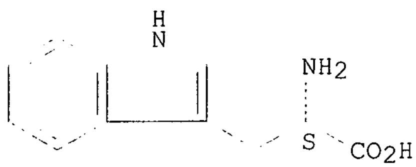
RN 63-91-2 HCAPLUS
CN L-Phenylalanine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



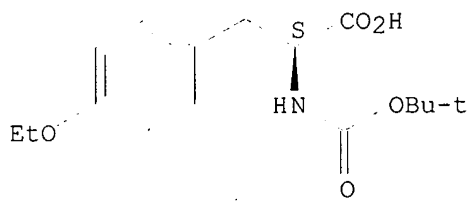
RN 73-22-3 HCAPLUS
CN L-Tryptophan (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 76757-91-0 HCAPLUS
CN L-Tyrosine, N-[(1,1-dimethylethoxy)carbonyl]-O-ethyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



=> d l11 bib abs hitstr 7

L11 ANSWER 7 OF 7 HCAPLUS
AN 1993:531523 HCAPLUS
DN 119:131523
TI nitrosylation of protein SH groups and amino acid residues for therapeutic uses
IN **Stamler, Jonathan**; Loscalzo, Joseph; Simon, Daniel; Singel, David
PA Brigham and Women's Hospital, USA
SO PCT Int. Appl., 114 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9309806	A1	19930527	WO 92-US9667	19921113
	W: AU, CA, JP, UA				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, SE				
	AU 9230715	A1	19930615	AU 92-30715	19921113
	EP 676964	A1	19951018	EP 92-924388	19921113
	R: CH, DE, DK, FR, GB, IT, LI, SE				
	US 5593876	A	19970114	US 94-287830	19940809
	AU 9728494	A1	19971016	AU 97-28494	19970703
	US 5863890	A	19990126	US 97-907217	19970806

PRAI US 91-791668 19911114
US 92-943835 19920914
WO 92-US9667 19921113
US 94-198854 19940217
US 94-287830 19940809
US 95-437868 19950509

AB Enzyme (e.g. tissue-type plasminogen activator, streptokinase, urokinase, and cathepsin), lipoprotein (e.g. VLDL, LDL, and HDL), Ig (e.g. IgG, IgA, IgM, IgD, and IgE), **Hb**, albumin, and myoglobin are **nitrosated** for use in regulating O delivery, protein function or cell proliferation, dilating blood vessels, treating cardiovascular disorders, relaxing non-vascular smooth muscle, lysing blood clot, etc.

IT **7782-44-7**, Oxygen, biological studies
RL: BIOL (Biological study)
(delivery of, regulation of, **nitrosated Hb** and myoglobin for)
RN 7782-44-7 HCAPLUS
CN Oxygen (8CI, 9CI) (CA INDEX NAME)

O═O

IT **10102-43-9**, Nitric oxide, biological studies
RL: BIOL (Biological study)
(delivery of, to specific site of the body, nitrosated enzyme and lipoprotein and other substance for)
RN 10102-43-9 HCAPLUS
CN Nitrogen oxide (NO) (8CI, 9CI) (CA INDEX NAME)

N=O

IT 7440-44-0, Carbon, biological studies 7727-37-9,
Nitrogen, biological studies
RL: BIOL (Biological study)
(nitric oxide delivery to site of, prepn. of S-nitroso-protein for)
RN 7440-44-0 HCAPLUS
CN Carbon (7CI, 8CI, 9CI) (CA INDEX NAME)

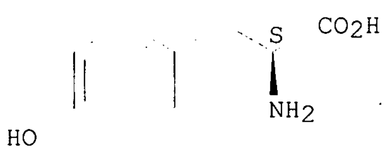
C

RN 7727-37-9 HCAPLUS
CN Nitrogen (8CI, 9CI) (CA INDEX NAME)

N≡N

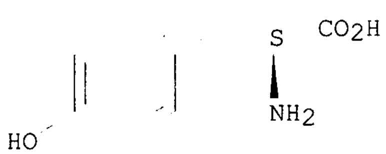
IT **60-18-4**, L-Tyrosine, reactions **60-18-4D**, L-Tyrosine,
nitrosylated **63-91-2**, Phenylalanine, reactions **63-91-2D**
, L-Phenylalanine, nitrosylated **73-22-3**, L-Tryptophan, reactions
72594-77-5 **72594-77-5D**, nitrosylated
RL: RCT (Reactant)
(nitrosation of)
RN 60-18-4 HCAPLUS
CN L-Tyrosine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



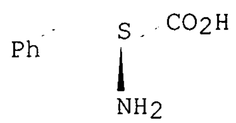
RN 60-18-4 HCAPLUS
CN L-Tyrosine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



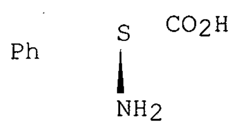
RN 63-91-2 HCAPLUS
CN L-Phenylalanine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



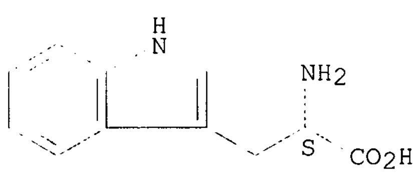
RN 63-91-2 HCAPLUS
CN L-Phenylalanine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



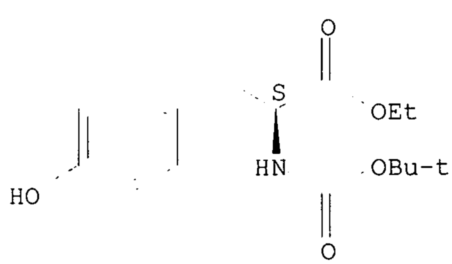
RN 73-22-3 HCAPLUS
CN L-Tryptophan (9CI) (CA INDEX NAME)

Absolute stereochemistry.



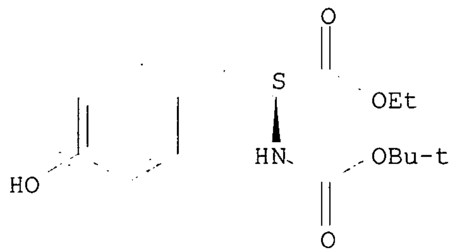
RN 72594-77-5 HCAPLUS
CN L-Tyrosine, N-[(1,1-dimethylethoxy)carbonyl]-, ethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 72594-77-5 HCAPLUS
CN L-Tyrosine, N-[(1,1-dimethylethoxy)carbonyl]-, ethyl ester (9CI) (CA INDEX NAME)

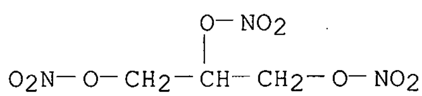
Absolute stereochemistry.



IT 55-63-0DP, Nitroglycerin, nitrosated 9002-01-1DP, S-nitrosated 9004-08-4DP, Cathepsin, S-nitrosated 9039-53-6DP, Urokinase, S-nitrosated 9047-22-7DP, Cathepsin B, S-nitrosated 139639-23-9DP, Tissue-type plasminogen activator, S-nitrosated
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, for therapeutic uses)

RN 55-63-0 HCAPLUS

CN 1,2,3-Propanetriol, trinitrate (9CI) (CA INDEX NAME)



RN 9002-01-1 HCAPLUS

CN Kinase (enzyme-activating), strepto- (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RN 9004-08-4 HCAPLUS

CN Cathepsin (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RN 9039-53-6 HCAPLUS

CN Kinase (enzyme-activating), uro- (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RN 9047-22-7 HCAPLUS

CN Cathepsin B (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RN 139639-23-9 HCAPLUS

CN Plasminogen activator, tissue-type (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT 139639-23-9, Tissue-type plasminogen activator
RL: RCT (Reactant)
(reaction of, in prepn. of S-nitrosated tissue-type plasminogen activator for therapeutic uses)

RN 139639-23-9 HCAPLUS

CN Plasminogen activator, tissue-type (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

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=> d l11 bib abs hitstr 8

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L16 ANSWER 1 OF 8 BIOSIS COPYRIGHT 1999 BIOSIS DUPLICATE 1
AN 1999:12407 BIOSIS
DN PREV199900012407
TI Nitrosative stress: Metabolic pathway involving the flavohemoglobin.
AU Hausladen, Alfred; **Gow, Andrew J.**; **Stamler, Jonathan S.** **(1)**
CS (1) Dep. Med., Howard Hughes Med. Inst., Duke Univ. Med. Cent., Durham, NC 27710 USA
SO Proceedings of the National Academy of Sciences of the United States of America, (Nov. 24, 1998) Vol. 95, No. 24, pp. 14100-14105.
ISSN: 0027-8424.
DT Article
LA English
AB Nitric oxide (NO) biology has focused on the tightly regulated enzymatic mechanism that transforms L-arginine into a family of molecules, which serve both signaling and defense functions. However, very little is known of the pathways that metabolize these molecules or turn off the signals. The paradigm is well exemplified in bacteria where S-nitrosothiols (SNO)-compounds identified with antimicrobial activities of NO synthase-elicit responses that mediate bacterial resistance by unknown mechanisms. Here we show that Escherichia coli possess both constitutive and inducible elements for SNO metabolism. Constitutive enzyme(s) cleave SNO to NO whereas bacterial hemoglobin, a widely distributed flavohemoglobin of poorly understood function, is central to the inducible response. Remarkably, the protein has evolved a novel heme-detoxification mechanism for NO. Specifically, the heme serves a dioxygenase function that produces mainly nitrate. These studies thus provide new insights into SNO and NO metabolism and identify enzymes with reactions that were thought to occur only by chemical means. Our results also emphasize that the reactions of SNO and NO with hemoglobins are evolutionary conserved, but have been adapted for cell-specific function.

L16 ANSWER 2 OF 8 BIOSIS COPYRIGHT 1999 BIOSIS DUPLICATE 2
AN 1998:89764 BIOSIS
DN PREV199800089764
TI Cell-free and erythrocytic S-nitrosohemoglobin inhibits human **platelet** aggregation.
AU Pawloski, John R.; Swaminathan, Rajesh V.; **Stamler, Jonathan S.** **(1)**
CS (1) Duke Univ. Med. Cent., Howard Hughes Med. Inst., Room 321 MSRB, Box 2612, Durham, NC 27710 USA
SO Circulation, (Jan. 27, 1998) Vol. 97, No. 3, pp. 263-267.
ISSN: 0009-7322.
DT Article
LA English
AB Background: Nitric oxide (NO) and related molecules are thought to inhibit human **platelet** aggregation by raising levels of cGMP. Methods and Results: Both oxidative stress (reactive oxygen species) and **hemoglobin** (**Hb**) seem to oppose **NO** effects. A major fraction of NO in the blood is bound to thiols of **Hb**, forming S-nitrosohemoglobin (**SNO-Hb**), which releases

the **NO** group on deoxygenation in the microcirculation. Here we show that (1) both cell-free and intraerythrocytic **SNO-Hb** (**SNO**-RBC) inhibit **platelet** aggregation, (2) the oxidation state of the hemes in Hb influences the response-SNOmetHb (which is functionally similar to SNO-deoxyHb) has greater **platelet** inhibitory effects than SNO-oxyHb, and (3) the mechanism of **platelet** inhibition by **SNO-Hb** is cGMP independent. Conclusions: We suggest that the RBC has evolved a means to counteract **platelet** activation in small vessels and the proaggregatory effects of oxidative stress by forming **SNO-Hb**.

L16 ANSWER 3 OF 8 BIOSIS COPYRIGHT 1999 BIOSIS DUPLICATE 3
AN 1998:71787 BIOSIS
DN PREV199800071787
TI Reactions between nitric oxide and haemoglobin under physiological conditions.
AU **Gow, Andrew J.; Stamler, Jonathan S. (1)**
CS (1) Howard Hughes Med. Inst., Dep. Med., Duke Univ. Med. Cent., Durham, NC 27710 USA
SO Nature (London), (Jan. 8, 1998) Vol. 391, No. 6663, pp. 169-173. ISSN: 0028-0836.
DT Article
LA English
AB The tenet of high-affinity nitric oxide (NO) binding to a haemoglobin (Hb) has shaped our view of haem proteins and of small diffusible signaling molecules. Specifically, NO binds rapidly to haem iron in Hb (k apprxeq 107 M-1 s-1) and once bound, the NO activity is largely irretrievable (Kd apprxeq 10-5 s-1); the binding is purportedly so tight as to be unaffected by O2 or CO. However, these general principles do not consider the allosteric state of Hb or the nature of the allosteric effector, and they mostly derive from the functional behaviour of fully nitrosylated Hb, whereas Hb is only partially nitrosylated in vivo. Here we show that oxygen drives the conversion of nitrosylhaemoglobin in the 'tense' T (or partially nitrosylated, deoxy) structure to S-nitrosohaemoglobin in the 'relaxed' R (or ligand-bound, oxy) structure. In the absence of oxygen, nitroxyl anion (NO-) is liberated in a reaction producing methaemoglobin. The yields of both S-nitrosohaemoglobin and methaemoglobin are dependent on the NO/Hb ratio. These newly discovered reactions elucidate mechanisms underlying NO function in the respiratory cycle, and provide insight into the aetiology of S-nitrosothiols, methaemoglobin and its related valency hybrids. Mechanistic reexamination of NO interactions with other haem proteins containing allosteric-site thiols may be warranted.

L16 ANSWER 4 OF 8 BIOSIS COPYRIGHT 1999 BIOSIS
AN 1998:459912 BIOSIS
DN PREV199800459912
TI Nitrosative stress: Metabolic pathways involving a flavohemoglobin (Denitrosolase.
AU Hausladen, Alfred; **Gow, Andrew J.; Stamler, Jonathan S.**
CS Howard Hughes Med. Inst., Dep. Med. and Cell Biol., Duke Univ. Med. Center, Durham, NC 27710 USA
SO Nitric Oxide, (1998) Vol. 2, No. 2, pp. 83.
Meeting Info.: Third International Conference on Biochemistry and Molecular Biology of Nitric Oxide Los Angeles, California, USA July 11-15,

1998 Nitric Oxide Society
. ISSN: 1089-8603.
DT Conference
LA English

L16 ANSWER 5 OF 8 BIOSIS COPYRIGHT 1999 BIOSIS
AN 1997:539938 BIOSIS
DN PREV199799839141
TI Nitric oxide in the respiratory cycle.
AU **Gow, A. J. (1)**; Eu, J. P.; McMahon, T. J.; Piantadosi, C. A.; **Stamler, J. S.**
CS (1) Univ. Pennsylvania, Philadelphia, PA USA
SO Japanese Journal of Pharmacology, (1997) Vol. 75, No. SUPPL. 1, pp. 18P.
Meeting Info.: 5th International Meeting on the Biology of Nitric Oxide Kyoto, Japan September 15-19, 1997
ISSN: 0021-5198.
DT Conference; Abstract
LA English

L16 ANSWER 6 OF 8 WPIDS COPYRIGHT 1999 DERWENT INFORMATION LTD
AN 98-467160 [40] WPIDS
DNN N98-363982 DNC C98-141579
TI Haemoglobin(s) modified with S-nitroso groups, and related compounds - used in treatment of e.g. ischaemic injury, hypertension, **angina** , reperfusion injury or inflammation.
DC B04 S03
IN **GOW, A J; STAMLER, J S**
PA (UYDU-N) UNIV DUKE MEDICAL CENT
CYC 21
PI WO 9834955 A1 980813 (9840)* EN 167 pp
RW: AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE
W: AU CA JP US
AU 9861502 A 980826 (9902)
ADT WO 9834955 A1 WO 98-US2383 980205; AU 9861502 A AU 98-61502 980205
FDT AU 9861502 A Based on WO 9834955
PRAI US 97-874992 970612; US 97-796164 970206
AN 98-467160 [40] WPIDS
AB WO 9834955 A UPAB: 981008
Treatment or prevention of diseases or medical disorders, which can be ameliorated by delivery of NO (or its biological equivalent) to tissues affected by the disease or disorder (in humans or animals), comprises administering: (i) nitrosyl-heme-containing donors of NO, (ii) a heme-based blood substitute and inhaled **NO**, (iii) CO-derivatised haemoglobin (**Hb**) and a **nitrosated Hb**; or
(iv) **Hb** beta -chains.

Also claimed are: (1) a method for delivering CO to tissues in animals or humans, comprising administering CO-derivatised Hb; (2) a method for treating shock in humans or animals, comprising administering Hb alpha -chains; (3) a method for measuring NO equivalents in S-nitrosohaemoglobin (SNH) and nitrosyl-Fe(II)-Hb (NFH) in blood comprising red blood cells (RBCs), comprising: (a) lysing the RBCs of a blood sample; (b) preparing a desalted protein fraction of the lysed RBCs;
(c) subjecting the fraction to photolysis, thus liberating NO from SNH and
NFH; and (d) quantitating the NO in the fraction by measuring a chemiluminescence signal generated by a chemical reaction between NO and ozone, thus measuring NO equivalents in SNH and NFH; (4) a method for assaying NO production in disease states, comprising: (a) lysing the RBCs

of a blood sample; (b) preparing a protein fraction of the lysed RBCs; (c) subjecting the fraction to photolysis, thus liberating NO from SNH and NFH; and (d) quantitating the NO in the fraction by measuring a chemiluminescence signal generated by a chemical reaction between NO and ozone; (5) a method for assaying NO equivalents in SNH and NFH in purified **Hb**, comprising measuring **NO** equivalents in the purified **Hb** by photolysis-chemiluminescence; (6) a method for measuring NO production in SNH and NFH in RBCs, comprising: (a) isolating washed RBCS from blood and lysing the RBCs to give a lysate; (b) desalting the lysate; and (c) measuring NO equivalents in the lysate by photolysis-chemiluminescence; (7) a method for measuring NO bound to NFH in RBCs, comprising: (a) making a protein fraction from the RBCs; (b) treating the protein fraction with HgCl2 followed by exposure to air; and (c) subjecting the protein fraction to photolysis of the NO ligand of NFH followed by detection of NO by chemiluminescence; (8) a method for assaying SNH, comprising: (a) isolating RBCs from blood and lysing the RBCs to give a lysate; (b) desalting the lysate; (c) contacting an aliquot of the lysate with mercury ions in excess of protein concentration, thus obtaining a mercury-treated aliquot and an untreated aliquot; (d) exposing the treated and untreated aliquots to oxygen; (e) measuring NO equivalents in the aliquots by photolysis-chemiluminescence; and (f) determining a quantity of SNH from the NO equivalents measured in (e); (9) a method for assaying thiol-bound NO in SNH in RBCs, comprising: (a) isolating washed RBCs from blood; (b) lysing the RBCs to give a lysate; (c) desalting the lysate; (d) dividing the lysate into (i) an aliquot contacted with mercury ions in excess of the protein concentration of the lysate and (ii) an aliquot which is untreated with mercury; (e) exposing both aliquots to oxygen; (f) isolating a mercury-treated low molecular weight fraction and an untreated low molecular weight fraction from the aliquots; (g) contacting the low molecular weight fractions with excess low molecular weight thiol under acidic conditions, thus producing S-nitrosothiol; (h) measuring NO liberated from S-nitrosothiol in the fractions of (g) by photolysis-chemiluminescence; and (i) determining a quantity of thiol-bound NO in SNH from a difference in measurements in (h); (10) a method for measuring SNH and NFH in RBCs, comprising: (a) isolating washed RBCs from blood; (b) lysing the RBCs; (c) desalting the lysate; and (d) measuring NO equivalents from the lysate by photolysis-chemiluminescence; (11) a method for making stable nitrosyl-deoxyhaemoglobin, comprising adding NO to deoxyhaemoglobin in an aqueous solution such that the ratio of NO to heme is below 1:100 or more than 0.75; (12) a method for making SNO-oxyhaemoglobin, comprising adding NO to an aqueous solution of oxyhaemoglobin and a buffer with a pK of at least 9.4, at a concentration of 10-200 mM, at pH 7.4; (13) a method for making nitrosyl-oxyhaemoglobin, comprising adding NO to oxyhaemoglobin in an aqueous solution such that the ratio of **NO** to **Hb** is below 1:30; (14) **Hb** conjugated to an **NO**-donor; (15) a composition comprising **Hb** and one or more **NO** donors; (16) nitrosylhaemoglobin conjugated to one or more electron acceptors; (17) a composition comprising nitrosylhaemoglobin and one or more electron acceptors; (18) Hb

conjugated to nitric oxide synthase; (19) a composition comprising Hb and nitric oxide synthase; (20) isolated erythrocytes comprising nitrosylhaemoglobin; (21) a method for making isolated erythrocytes comprising nitrosylhaemoglobin comprises incubating deoxygenated erthrocytes in a solution comprising NO; (22) a method for assaying SNH comprising (a)-(c) as in (9) followed by: (d) contacting an aliquot of
the
lysate of (c) with mercury ions in excess over protein concentration ,
to
obtain a mercury-treated aliquot and an untreated aliquot; (e) exposing the mercury treated aliquot and the untreated aliquot to oxygen; (f) measuring NO equivalents in the two aliquots by photolysis chemoluminescence; (g) determining the quantity of SNH from the NO equivalents measured in (f); (23) a method for measuring SNH and NFH in a sample comprising (a)-(c) as in (9) followed by the step of measuring NO equivalents in the lysate by photolysis-chemoluminescence; (24) a method for assaying NFH comprising (a)-(f) as in (22) where step (f) gives information about SNH and NFH + SNH concentration NFH concentration is assayed by subtracting SNH concentration form the figure for NFH = SNH concentration.

USE - The inventions can be used for producing and isolating S-nitrosohaemoglobin ((**SNO-Hb**) e.g. for use in
therapy) by reaction of Hb with S-nitrosothiol in procedures which avoid oxidation of the heme. The methods can also be used for producing isolated, **nitrosated** and nitrated derivatives of **Hbs**
in which the heme iron may or may not be oxidised. The methods can also
be
used as methods of therapy for conditions requiring oxidation, scavenging of free radicals, or release of NO+ groups to tissues, involving administration of compositions comprising **SNO-Hb**,
thiols and/or **NO**-donating agents. Examples of such conditions incude ischaemic injury, hypertension, **angina**, reperfusion injury, inflammation or diseases characterised by **thrombosis**.
Dwg.0/26

L16 ANSWER 7 OF 8 WPIDS

AN 97-212535 [19] WPIDS
CR 97-202348 [18]; 97-212491 [19]
DNC C97-068560
TI Nitrosated or nitrated haemoglobin(s), their prepn. and uses - e.g. to oxygenate, to scavenge free radicals or release nitric oxide gps. to tissues and treat ischaemic injury, hypertension, **angina**.
DC B04 B05 D22
IN **STAMLER, J S**
PA (UYDU-N) UNIV DUKE MEDICAL CENT
CYC 75
PI WO 9710265 A1 970320 (9719)* EN 83 pp
RW: AT BE CH DE DK EA ES FI FR GB GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE HU IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM TR TT UA UG US UZ VN
AU 9670198 A 970401 (9730)
EP 850251 A1 980701 (9830) EN
R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
ADT WO 9710265 A1 WO 96-US14659 960913; AU 9670198 A AU 96-70198 960913; EP 850251 A1 EP 96-931549 960913, WO 96-US14659 960913
FDT AU 9670198 A Based on WO 9710265; EP 850251 A1 Based on WO 9710265
PRAI US 96-667003 960620; US 95-3801 950915; US 96-616371 960315

AN 97-212535 [19] WPIDS
CR 97-202348 [18]; 97-212491 [19]
AB WO 9710265 A UPAB: 970512
Delivering nitro-oxide to in a mammal comprises administering a low molecular weight nitrosating agent to the mammal.

Also claimed are: (1) a method for preparing S-nitroso-haemoglobin (**SNO-Hb**)(FeII) specifically S-**nitrosylated** on thiol groups, by incubating excess **nitrosating** agent with purified **Hb** in the absence of O2;

(2) a method for preparing **SNO-Hb**(FeII) O2, specifically S-**nitrosylated** on thiol groups (without oxidation of heme Fe) by incubating excess **nitrosating** agent with purified **Hb** in the presence of O2;

(3) a method for regulating delivery of O2 and NO, in various redox forms, by administering a mixture of a low molecular weight thiol or nitroso-thiol and **Hb** or **nitrosated Hb**;

(4) use of a blood substitute comprising **nitrosated Hb** for delivering **NO**, for scavenging oxygen free radicals and NO and reducing blood pressure;

(5) a blood substitute comprising **nitrosated** or nitrated **Hb** and its uses;

(6) a method for regulating **platelet** activation by admin. of a composition comprising a substance (II) which controls the allosteric equilibrium or spin state of Hb;

(7) methods for forming poly-**nitrosated Hb** and poly-nitrated **Hb** (see 'Preferred Method'), and

(8) a composition comprising poly-**nitrosated Hb**.

USE - The method is used to increase the O2 delivery capacity of Hb in a mammal suffering from shock, **angina**, stroke, reperfusion injury, acute lung injury, sickle cell anaemia and infection of red blood cells.

S-nitroso-thiol (RSNO) can be used to treat a blood borne disease (e.g. malaria) by isolating red blood cells, treating them with RSNO and re-administering them to the patient.

Nitrosated or nitrated **Hb** can be used to treat heart, brain, vascular and lung diseases; atherosclerosis and inflammation; also diseases resulting from **platelet** activation or adherence (e.g. **myocardial** infarction, pulmonary **thromboembolism**, cerebral **thromboembolism**, **thrombophlebitis**, **sepsis** and unstable **angina**).

Nitrosated Hb can also be used to treat stroke, **angina**, respiratory distress syndrome, and diseases or conditions with abnormalities of NO and oxygen metabolism (e.g. heart and lung diseases, sickle-cell anaemia, stroke, **sepsis** and organ transplantation); and to prevent **thrombus** formation.

Nitrosated Hb is also used to keep organs alive ex vivo to use for transplantation (all claimed).
Dwg.0/11

L16 ANSWER 8 OF 8 WPIDS
AN 94-332842 [41] WPIDS
DNN N94-261274 DNC C94-151360
TI Admin of e.g. nitric oxide by inhalation - is useful for treatment of pulmonary emboli, **angina** pectoris, acute respiratory distress syndrome, etc..
DC B05 B06 B07 P34
IN FROSTELL, C G; HEDENSTIERNA, G; HOGMAN, M E; LOSCALZO, J; **STAMLER, J S**; FROSTELL, C

PA (BGHM) BRIGHAM & WOMENS HOSPITAL
CYC 21
PI WO 9422499 A1 941013 (9441)* EN 28 pp
RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE
W: AU CA JP
AU 9464968 A 941024 (9505)
US 5427797 A 950627 (9531) 7 pp
EP 692984 A1 960124 (9609) EN
R: CH DE FR GB IE IT LI SE
JP 09500609 W 970121 (9713) 19 pp
AU 690109 B 980423 (9828)
ADT WO 9422499 A1 WO 94-US3561 940331; AU 9464968 A AU 94-64968 940331; US 5427797 A US 93-43653 930406; EP 692984 A1 EP 94-912377 940331, WO 94-US3561 940331; JP 09500609 W JP 94-522387 940331, WO 94-US3561 940331; AU 690109 B AU 94-64968 940331
FDT AU 9464968 A Based on WO 9422499; EP 692984 A1 Based on WO 9422499; JP 09500609 W Based on WO 9422499; AU 690109 B Previous Publ. AU 9464968, Based on WO 9422499
PRAI US 93-43653 930406
AN 94-332842 [41] WPIDS
AB WO 9422499 A UPAB: 941206
The following are claimed: (A) methods for (i) systemic prevention or treatment of systemic blood **platelet** aggregation and coagulation, (ii) prevention or treatment of acute coronary syndromes including **angina** pectoris or (iii) prevention or treatment of acute respiratory distress syndrome, comprising admin., by the inhalation route, of a cpd. selected from nitric oxide and cpds. that deliver nitric oxide upon admin..

Also claimed is prevention or treatment of pulmonary emboli comprising admin., to the lung, of a pharmaceutical compsn. comprising a cpd. selected from nitric oxide and cpds. which deliver nitric oxide upon admin..

Dosage is 1 pg-1 mg per kg of body wt.

Dwg.0/1
ABEQ US 5427797 A UPAB: 950810
Systemic treatment to inhibit blood **platelet** aggregation and coagulation and to treat respiratory distress syndrome and elevate NO level in systemic circulation comprises inhalation of NO or NO-releasing cpd., viz. S-nitrosothiols, S-nitroso-proteins, NONOnates, Fe-nitosyls opt. with thiolate ligands, thionitrites, thionitrates, sydnonimines, furoxans, nitrosonium salts, and organic nitrates and nitrites.

ADVANTAGE - The inhalation route avoids adverse effects of **No** with active O2 species and with **hemoglobin**. giving effective therapy. Dosage is e.g. 1pg-1mg/kg.

Dwg.0/1

=> d 1-9 bib abs

L19 ANSWER 1 OF 9 HCAPLUS COPYRIGHT 1999 ACS
AN 1998:515515 HCAPLUS
DN 129:230051
TI Assessment of the safety of supplementation with different amounts of vitamin E in healthy older adults
AU Meydani, Simin Nikbin; Meydani, Mohsen; Blumberg, Jeffrey B.; Leka, Lynette S.; Pedrosa, Marcos; Diamond, Richard; Schaefer, Ernst J.
CS Jean Mayer USDA Human Nutrition Research Center on Aging, Tufts University, Boston, MA, 02111, USA
SO Am. J. Clin. Nutr. (1998), 68(2), 311-318
CODEN: AJCNAC; ISSN: 0002-9165
PB American Society for Clinical Nutrition
DT Journal
LA English
AB Daily supplementation with 800 IU (727 mg) vitamin E for 30 days does not adversely affect healthy elderly persons. The effects of 4-mo daily supplementation with 60, 200, or 800 IU (55, 182, 727 mg) all-rac-.alpha.-tocopherol on general health, nutrient status, liver enzymes, thyroid hormone concns., creatinine concns., serum autoantibodies, neutrophil killing of Candida albicans, and bleeding time were studied in 88 healthy subjects >65 yr of age. No side-effects were reported by the subjects. Vitamin E supplementation had no effect on body
wt., blood plasma total proteins, albumin, glucose, plasma lipids, lipoprotein profile, total bilirubin, alk. phosphatase, serum aspartate aminotransferase, serum alanine aminotransferase, lactate dehydrogenase, serum urea **nitrogen**, total red blood cells, white blood cells, white blood cell differential counts, blood **platelet no**
., bleeding time, **Hb**, hematocrit, thyroid hormones, or urinary and serum creatinine concns. The values from all supplemented groups were
within normal ranges for older adults and were not different from values in the placebo group. Vitamin E supplementation had no significant effects on blood plasma concns. of other antioxidant vitamins and minerals, glutathione peroxidase, superoxide dismutase, or total homocysteine. There was no effect of vitamin E on blood serum nonspecific
Ig concns. or anti-DNA and anti-thyroglobulin antibodies. The cytotoxic ability of neutrophils against Candida albicans was not compromised. Thus, 4-mo daily supplementation with 60-800 IU vitamin E had no adverse effects. These results are relevant for detg. the risk/benefit ratios for
vitamin E supplementation.

L19 ANSWER 2 OF 9 HCAPLUS COPYRIGHT 1999 ACS
AN 1996:726427 HCAPLUS
DN 126:5732
TI Synergic effects of NO and oxygen free radicals in the injury of ischemia-reperfused myocardium ESR studies on NO free radicals generated from ischemia-reperfused myocardium
AU Zhao, Baolu; Shen, Jiangang; Hu, Jungai; Wan, Qian; Xin, Wenjuan
CS Institute Biophysics, Chinese Academy Sciences, Beijing, 100101, Peop. Rep. China
SO Sci. China, Ser. C: Life Sci. (1996), 39(5), 491-500
CODEN: SCCLFO; ISSN: 1006-9305

PB Science in China Press
DT Journal
LA English
AB The ESR signal of **NO** bound to **Hb** was detected during the ischemia-reperfusion of **myocardium** with low temp. ESR technique, and the synergic effects of NO and oxygen free radicals in the injury of the process were studied with this technique. Oxygen free radicals and **NO** bound to .beta.-subunit of **Hb** (.beta.-**NO** complex) could be detected simultaneously in the ischemia-reperfused **myocardium**. Those signals could not be detected from the normal myocardium even in the presence of L-arginine. However, those signals could be detected and were dose-dependent with L-arginine in the ischemia-reperfused myocardiums and the signal could be suppressed with the inhibitor of NO synthetase, NG-**nitroL** -arginine methylester (NAME). Measurement of the activities of lactate dehydrogenase (LDH) and creatine kinase (CK) in the coronary artery effluent of ischemia-reperfused heart showed that L-arginine at lower concn. (<1 mmol/L) could protect the heart from the ischemia-reperfusion injury but at higher concn. aggravate the injury. Addn. of NAME to the reperfusion soln. could also protect the myocardium. Addn. of xanthine (X)/xanthine oxidase (XO) or Fe^{2+}/H_2O_2 to the reperfusion soln. increased the prodn. of NO and oxygen free radicals and the ischemia-reperfused injury simultaneously. Addn. of superoxide dismutase (SOD) and catalase decreased the prodn. of NO and oxygen free radicals and the ischemia-reperfusion injury.

L19 ANSWER 3 OF 9 HCAPLUS COPYRIGHT 1999 ACS
AN 1996:546910 HCAPLUS
DN 125:219520
TI Two mechanisms for platelet-mediated killing of tumor cells: one cyclo-oxygenase dependent and the other nitric oxide dependent
AU Okada, M.; Sagawa, T.; Tominaga, A.; Kodama, T.; Hitsumoto, Y.
CS Dep. Clinical Lab. Technology, Ehime College of Health Science, Ehime, Japan
SO Immunology (1996), 89(1), 158-164
CODEN: IMMUAM; ISSN: 0019-2805
DT Journal
LA English
AB The authors tried to identify the cytotoxic effectors in platelet-mediated tumor cell killing, using 2 tumor cell lines K562 (a chronic myelogenic leukemic cell line) and LU99A (a lung cancer cell line), which are both sensitive to platelet cytotoxicity. Cyclo-oxygenase inhibitors, acetylsalicylic acid (ASA) and indomethacin, effectively inhibited the platelet-mediated killing of K562 cells, but not that of LU99A cells. In contrast, inhibitors of the nitric oxide (**NO**) pathway, NG-**nitro**-L-arginine (L-NA), **Hb** and methylene blue, reduced the cytotoxic activity of **platelets** against LU99A, but not against K562. Synthetic analogs of platelet cyclo-oxygenase products thromboxane A2/prostaglandin H2 (TXA2/PGH2) exerted cytotoxicity against K562 cells but not against LU99A cells. Electron microscopic study showed that TXA2/PGH2 analogs induced bleb formation and disruption of the plasma membrane of K562 cells. K562 cells enhanced the prodn. of TXA2 by platelets, as inferred from the accumulation of thromboxane B2 (TXB2), a spontaneous hydrolysis product of TXA2. LU99A cells had no such effects. Thus, platelets kill these 2 tumor cell lines through different mechanisms. In K562, the cyclo-oxygenase products TXA2/PGH2 possibly play

a role, but in LU99A the NO pathway seems to be involved.

L19 ANSWER 4 OF 9 HCAPLUS COPYRIGHT 1999 ACS
AN 1996:327287 HCAPLUS
DN 125:30783
TI Effects of nitric oxide/EDRF on platelet surface glycoproteins
AU Michelson, Alan D.; Benoit, Stephen E.; Furman, Mark I.; Breckwoldt, William L.; Rohrer, Michael J.; Barnard, Marc R.; Loscalzo, Joseph
CS Dep. Pediatrics, Med. Cell Biology, and Surgery, Univ. Massachusetts Med. Sch., Worcester, 01655, USA
SO Am. J. Physiol. (1996), 270(5, Pt. 2), H1640-H1648
CODEN: AJPHAP; ISSN: 0002-9513
DT Journal
LA English
AB We examd. the effects of nitric oxide (NO)/endothelium-drived relaxing factor (EDRF) on platelet surface glycoproteins (GP). As detd. by flow cytometry, in both a washed platelet system and platelet-rich plasma, the EDRF congener (S-**nitroso**-N-acetylcysteine) markedly inhibited both the thrombin-induced and the (stable thromboxane A2 analog) U-46619-induced upregulation of P-selectin (.alpha.-granule protein), CD63 (lysosomal protein), and the GPIIb-IIIa complex (fibrinogen receptor) but minimally inhibited downregulation of the GPIb-IX complex (von Willebrand factor receptor). The inhibitory effects of EDRF were markedly reduced in whole blood or by the addn. of washed erythrocytes. Platelets in whole blood were still responsive to guanosine 3',5'-cyclic monophosphate (cGMP), as shown by complete inhibition of P-selectin upregulation by the stable analog N6,2'-O-dibutyryl cGMP. These data suggest that 1) cGMP neg. regulates the platelet surface expression of P-selectin, CD63, and the GPIIb-IIIa complex but not the **platelet** surface expression of the GPIb-IX complex and 2) **Hb** within erythrocytes inhibits the effects of EDRF/**NO** on platelet surface glycoproteins.

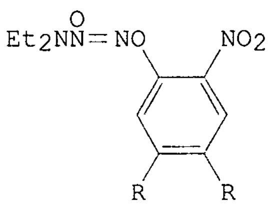
L19 ANSWER 5 OF 9 HCAPLUS COPYRIGHT 1999 ACS
AN 1996:60757 HCAPLUS
DN 124:107481
TI Nitric oxide and prostacyclin modulate the alterations in cardiac action potential duration mediated by platelets during ischemia
AU Boulielmos, Nicos V.; Enayat, Zinat E.; Sheridan, Desmond J.; Cohen, Hannah; Flores, Nicholas A.
CS Academic Cardiology Unit, St. Mary's Hospital Medical School, London, W2 1NY, UK
SO Cardiovasc. Res. (1995), 30(5), 788-98
CODEN: CVREAU; ISSN: 0008-6363
DT Journal
LA English
AB The effects of alterations of nitric oxide (NO) and prostacyclin (PGI2) availability on platelet-mediated electrophysiol. effects were examd.during myocardial ischemia. Transmembrane action potentials and electrograms were recorded from isolated, Langendorff-perfused guinea-pig hearts during normal perfusion, global myocardial ischemia and reperfusion during infusion of washed human platelets. Expts. were performed in the presence of 100 .mu.M NG-**nitro**-L-arginine Me ester (L-NAME), 30 .mu.M L-arginine, 10 .mu.M Hb, 100 .mu.M sodium **nitroprusside** and 2.3 nM iloprost, or using hearts obtained from DL-lysine monoacetylsalicylate (Aspisol, 50 mg.cntdot.kg-1 i.p.)-treated animals. Perfusion with L-NAME and Hb increased perfusion pressure by 33% and 23%

while sodium **nitroprusside** and iloprost reduced it (17%, and 24%). In the absence of platelets, these compds. had no effect on arrhythmogenesis, but in the presence of platelets L-NAME reduced the onset time of ventricular tachycardia during ischemia from 19.4 min to 12.9 min, and accentuated the ischemia-induced redn. of action potential duration at 95% repolarization (APD95): 95(6) vs. 115(5) ms, at 25 min. Sodium **nitroprusside** in the presence of platelets attenuated the ischemia-induced redn. in APD95, while iloprost in the presence of platelets was antiarrhythmic (ventricular fibrillation 25 vs. 75%) and attenuated the redn. in APD95 during ischemia 115(4) vs. 94(4) ms, at 20 min. Infusion of platelets into hearts obtained from DL-lysine-mono-acetylsalicylate-treated guinea-pigs accentuated the ischemia-induced redn. in APD95 (94(4) vs. 119(7) ms, at 20 min) and this was reversed by sodium **nitroprusside** (117(7) ms, at 20 min). L-NAME and **Hb** had **no** effect on the aggregatory responses of the **platelets** of 5 .mu.M ADP and 4 .mu.g.cntdot.ml-1 collagen, while sodium **nitroprusside** and iloprost ablated the responses to ADP and reduced the responses to collagen (max. height of the aggregatory response reduced by 75 and 84%, resp., both). Inhibition of NO and PGI2 synthesis exacerbates the redn. in cardiac action potential duration assocd. with platelet activation during ischemia, while provision of exogenous NO and PGI2 attenuates the redn. in cardiac action potential with platelet activation during ischemia, while provision of exogenous NO and PGI2 attenuates the redn. in cardiac action potential duration. Provision of exogenous NO and PGI2 (as iloprost) was assocd. with inhibition of platelet reactivity.

L19 ANSWER 6 OF 9 HCAPLUS
AN 1995:834005 HCAPLUS
DN 123:252592
TI The hematology and blood-chemistry of Orangutan under artificial feeding environment
AU Lee, Wei-Ming; Chou, Shyh-Renn; Shyu, Ching-Lin; Tung, Kwong-Chung
CS Dep. Veterinary Med., Natl. Chung Hsing Univ., Taichung, 402, Taiwan
SO Zhonghua Minguo Shouyi Xuehui Zazhi (1995), 21(3), 160-8
CODEN: CKSCDN; ISSN: 0253-9179
DT Journal
LA Chinese
AB Orangutan, an endangered species, is protected by the R.O.C. government in
Taiwan. For the time being, data concerning the values of hematol. and blood-chem. for Orangutan are unavailable. The purpose of this study was to establish the hematol. and blood-chem. values for these animals. After
their examn. the results were as follows: (1) No. of total WBC 13.72.times.103/uL, (2) **No**. of total RBC 4.74.times.106/uL, (3) **Hb** 10.34 g/dL, (4) hematocrits 32.63 %, (5) **platelet** 217.76.times.103/UL, (6) mean corpuscular vol. 69.36 fL, (7) mean corpuscular Hb 21.84 pg, (8) mean corpuscular Hb concn. 31.58 g/dL, (9) blood glucose 92.36 mg/dL, (10) total protein 6.5 g/dL, (11) albumin 2.53 g/dL, (12) total bilirubin 0.3 mg/dL, (13) aspartate aminotransferase 13.82 U/L, (14) alanine aminotransferase 11.06 U/L, (15) alk. phosphatase 529.25 U/L, (16) cholesterol 150.13 mg/dL, (17) triglyceride 73.94 mg/dL, (18) lactic dehydrogenase 506.81 U/L, (19) uric acid 1.99 mg/dL, (20) BUN 19.93 mg/dL, (21) creatinine 0.75 mg/dL, (22) thyroxine 3.29 .mu.g/dL, (26) Mg 1.83 mEq/L, (27) Na 130.75 mEq/L, (28) K 5.09 mEq/L, and (29) Cl 92.31 mEq/L.

L19 ANSWER 7 OF 9 HCAPLUS

AN 1994:473342 HCAPLUS
DN 121:73342
TI Caged nitric oxide. Stable organic molecules from which nitric oxide can be photoreleased
AU Makings, Lewis R.; Tsien, Roger Y.
CS Howard Hughes Med. Inst., Univ. California, San Diego, La Jolla, CA, 92093-0647, USA
SO J. Biol. Chem. (1994), 269(9), 6282-5
CODEN: JBCHA3; ISSN: 0021-9258
DT Journal
LA English
GI



I, R=H
II, R=OMe
III, R=OCH_2CO_2Et
IV,, R=OCH_2CO_2K
V, R=$OCH_2CO_2CH_2OAc$

AB The authors report the synthesis and testing of a series of "caged" nitric oxide compds. that are stable indefinitely in oxygen-contg. solns. until photolyzed by UV irradn., whereupon they release nitric oxide (NO) with quantum yields of .DELTA.5% for I and .DELTA.2% for compds. II-V. After a flash, NO release is complete within 5 ms, so that precise temporal control of NO release is possible. NO donor IV includes two carboxylate neg. charges at physiol. pH, which reduce membrane permeability and enable photolytic generation of NO to be selectively confined to either extracellular or intracellular compartments. Esterification of these carboxyls with acetoxymethyl groups produces V, which is membrane-permeant and intracellularly hydrolyzable. Therefore, large populations of intact cells can be conveniently intracellularly loaded with "caged" NO donor IV by incubation with V. The biol. efficacy of these NO donors and their abs. dependence on UV-irradn. was demonstrated by inhibition of thrombin-stimulated platelet aggregation. Extracellular **Hb** blocked the effects of **NO** generated outside but not inside **platelets**, verifying the sidedness of the NO donors and the limited spatial range of NO action. These mols. should permit precise spatial, temporal, and concn. control of NO release for investigation of its important biol. functions.

L19 ANSWER 8 OF 9 HCAPLUS
AN 1991:556199 HCAPLUS
DN 115:156199
TI Nitric oxide hemoglobin in mice and rats in endotoxic shock
AU Wang, Qizhi; Jacobs, Judith; DeLeo, Joyce; Kruszyna, Harriet; Kruszyna, Robert; Smith, Roger; Wilcox, Dean
CS Dep. Pharmacol. Toxicol., Dartmouth Med. Sch., Hanover, NH, USA
SO Life Sci. (1991), 49(11), PL55-PL60
CODEN: LIFSAK; ISSN: 0024-3205
DT Journal

LA English
AB Mice given i.p. bacterial endotoxin (LPS) at 10 mg/kg showed a statistically significant decrease in plasma glucose and an increase in hematocrit at 2 h after injection. Glucose was still decreased at 4 h, but the hematocrit had returned to control values. **Nitrosylated** Hb (HbNO) was detected at 3, but not at 2 h. By 4 h it had increased 5-fold. When N-monomethylarginine (NMMA) at 100 mg/kg, i.p. was given 2
h
after LPS in mice, the HbNO concn. at 4 h was reduced, but the hypoglycemia was worsened because NMMA itself produced hypoglycemia.
Rats
given i.v. LPS, 20 mg/kg, showed a fleeting, transient rise in mean arterial pressure (MAP) lasting only a few min. Thereafter, the MAP tended to drift slowly downward over 4 h, but when the MAP at 30 min intervals was compared to the pre-LPS MAP, there were no differences. Plasma glucose in unanesthetized rats was elevated at 1 h, back to
control
at 2 h, and decreased at 3 h. HbNO was detected as early as 1 h after injection. By 2 h the HbNO concns. exceeded the highest levels found in mice, and they were still increasing as late as 5 h after injection. Unanesthetized rats showed toxic signs and 3/12 rats died with 4 h of LPS administration. These results are consistent with a model for endotoxic shock in which LPS stimulates an inducible pathway for NO synthesis.

L19 ANSWER 9 OF 9 HCAPLUS COPYRIGHT 1999 ACS
AN 1976:38647 HCAPLUS
DN 84:38647
TI Effect of right atrial pacing and **nitroglycerin** on myocardial oxygen balance
AU Warltier, David C.; Gross, Garrett J.; Hardman, Harold F.
CS Dep. Pharmacol., Med. Coll. Wisconsin, Milwaukee, Wis., USA
SO Eur. J. Pharmacol. (1975), 34(1), 229-32
CODEN: EJPHAZ
DT Journal
LA English
AB Whereas atrial pacing produced an increase in **myocardial** O consumption (MVO2) in isolated canine hearts and **no** change in the affinity of **hemoglobin** for O [7782-44-7] (P-50), an intracoronary infusion of **nitroglycerin** [55-63-0] decreased both MVO2 and the affinity of hemoglobin for O (increased P-50) in coronary venous blood. Under conditions of a const. coronary blood flow, **nitroglycerin** may benefit an hypoxic myocardium by reducing O demand and by increasing availability of O for rapid diffusion to tissue by increasing P-50.

=> D BIB ABS 1-26

L27 ANSWER 1 OF 21 HCAPLUS COPYRIGHT 1999 ACS
AN 1998:418447 HCAPLUS
DN 129:200829
TI Nitric oxide and cardiac contraction: clinical studies
AU Paulus, Walter J.
CS Cardiovascular Center, O.L.V. Ziekenhuis, Aalst, B-9300, Belg.
SO Endothelial Cell Res. Ser. (1997), 2(Endothelial Modulation of Cardiac Function), 35-51
CODEN: ECRSFY; ISSN: 1384-1270
PB Harwood Academic Publishers
DT Journal; General Review
LA English
AB A review with 89 refs. Endothelial release of nitric oxide (NO) is an important control mechanism of vascular tone. Nitric oxide released from the endothelial lining of the coronary vasculature also influences **myocardial** performance. In isolated papillary muscles and in ejecting guinea-pig hearts, substance P, which releases NO from endothelial cells, shortened **myocardial** contraction through a relaxation hastening effect. Similar findings were obsd. with exogenous NO-donor substances such as sodium nitroprusside. These observations were
recently extended to the clin. setting because of demonstration in man of **myocardial** contractile effects of both exogenous and endogenous NO. In healthy control subjects, bicoronary infusion of the NO-donor sodium nitroprusside, reduced LV peak and end-systolic pressures through a
relaxation-hastening effect and increased LV diastolic distensibility. Similar observations were made in transplant recipients and in patients with aortic stenosis. The occasional observation of a larger LV end-diastolic vol. during i.v. NO-donor infusion supports the presence of direct **myocardial** relaxant effects of NO even during i.v. administration of NO-donors. Direct **myocardial** effects of NO could not be demonstrated in normal subjects or in heart failure patients during inhalation of NO probably because of rapid inactivation of **NO** by **Hb** in the pulmonary circulation. In healthy control subjects and in transplant recipients, bicoronary infusion of substance P influenced LV performance in a similar way as bicoronary infusion of sodium nitroprusside by reducing LV peak and end-systolic pressures, by hastening the onset of LV relaxation and by increasing LV diastolic distensibility. These effects were attributed to a paracrine **myocardial** action of NO, released by substance P from the coronary endothelium and were potentiated in transplant recipients by simultaneous intracoronary infusion of L-arginine or by i.v. infusion of dobutamine. Because of recent demonstration of **myocardial** expression of inducible NO-synthase in certain cardiomyopathies, the cardiodepression obsd. in these conditions was linked to **myocardial** prodn. of NO. The functional consequence of NO produced by inducible NO-synthase remains
however unclear because, in contrast to NO derived from NO-donor or endothelial cells, expression of inducible NO-synthase impairs **myocardial** relaxation. **Myocardial** relaxant effects of endothelially released NO are relevant to diastolic LV performance both acutely and chronically. Acute increases in LV workload augment coronary flow and increase endothelial release of NO, which through its paracrine **myocardial** action lowers LV filling pressures to promote subendocardial perfusion and hasten the onset of LV relaxation to prolong

diastolic coronary perfusion time. Chronic enhancement of coronary endothelial release of NO as a result of chronic exercise or pacing could relate to the increased LV diastolic distensibility obsd. in athlete's heart or in tachycardia-induced cardiomyopathy. Chronic redn. of coronary endothelial release of NO, as occurs with aging or after transplantation, could explain reduced diastolic LV distensibility in the elderly or in transplant recipients.

L27 ANSWER 2 OF 21 HCAPLUS COPYRIGHT 1999 ACS
AN 1998:77653 HCAPLUS
DN 128:215878
TI Inactivation of the cardiac ryanodine receptor calcium release channel by nitric oxide
AU Zahradnikova, Alexandra; Minarovic, Igor; Venema, Richard C.; Meszaros, Laszlo G.
CS Department of Physiology & Endocrinology, Medical College of Georgia, Augusta, GA, 30912, USA
SO Cell Calcium (1997), 22(6), 447-453
CODEN: CECADV; ISSN: 0143-4160
PB Churchill Livingstone
DT Journal
LA English
AB We have recently reported (Meszaros L.G.; et al., 1996) that nitric oxide (NO) reduces the activity of the skeletal muscle ryanodine receptor Ca2+ release channel (RyRC), a principal component of the excitation-contraction coupling machinery in striated muscles. Since (i) as shown here, we have obtained evidence which indicates that the NO synthase (eNOS) of cardiac muscle origin co-purified with RyRC-contg. sarcoplasmic reticulum (SR) fractions; and (ii) the effects of NO donors on the release channel, as well as on cardiac function, appear somewhat contradictory, we have made an attempt to investigate the response of the cardiac RyRC to NO that is generated in situ from L-arginine in the NOS reaction. We found that L-arginine-derived NO inactivates Ca2+ release from cardiac SR and reduces the steady-state activity (i.e. open probability) of single RyRCs fused into a planar lipid bilayer. This redn. was prevented by NOS inhibitors and the **NO** quencher **Hb** and was reversed by 2-mercaptoethanol. We thus conclude that: (i) in isolated SR prepns., it is possible to assess the effects of NO that is generated from L-arginine in the NOS reaction; and (ii) cardiac RyRC responds to NO in a manner which is identical to that we have previously found with the skeletal channel. These findings suggest that the direct modulation of the RyRC by NO is a signaling mechanism which likely participates in earlier demonstrated NO-induced **myocardial** contractility changes.

L27 ANSWER 3 OF 21 HCAPLUS COPYRIGHT 1999 ACS
AN 1997:514843 HCAPLUS
DN 127:218413
TI cAMP induces heme oxygenase-1 gene expression and carbon monoxide production in vascular smooth muscle
AU Durante, William; Christodoulides, Nick; Cheng, Karen; Peyton, Kelly J.; Sunahara, Roger K.; Schafer, Andrew I.
CS Houston Veterans Affairs Medical Center and Department of Medicine, Baylor College of Medicine, Houston, TX, 77030, USA

SO Am. J. Physiol. (1997), 273(1, Pt. 2), H317-H323
CODEN: AJPHAP; ISSN: 0002-9513
PB American Physiological Society
DT Journal
LA English
AB Recent studies indicate that vascular smooth muscle cells generate carbon monoxide (CO) via the action of heme oxygenase (HO). Because adenosine 3',5'-cyclic monophosphate (cAMP) is an important intracellular signaling mol. in the regulation of vascular cell function, we examd. whether this second messenger modulates the expression of HO and the prodn. of CO by rat aortic smooth muscle cells. Treatment of smooth muscle cells with the membrane-permeable cAMP deriv. dibutyryl cAMP or with compds. that increase intracellular cAMP levels (isoproterenol and forskolin) resulted in a concn.- and time-dependent increase in the levels of HO-1 mRNA and protein, whereas the expression of HO-2 remained unchanged. Both actinomycin D and cycloheximide blocked the basal expression of HO-1 mRNA and protein and prevented the cAMP-mediated induction of HO-1. Incubation of **platelets** with cAMP-treated smooth muscle cells resulted in a significant increase in **platelet** cGMP concn. that was partially reversed by treatment of smooth muscle cells with the nitric oxide synthase inhibitor NG-monomethyl-L-arginine or the HO blocker zinc protoporphyrin-IX. However, the combined addn. of these two inhibitors to cAMP-treated smooth muscle cells or the addn. of the CO and **NO** scavenger **Hb** to **platelets** completely blocked the stimulatory effect on **platelet** cGMP levels. These results demonstrate that cAMP induces the expression of the HO-1 gene and stimulates the formation of CO and NO in vascular smooth muscle cells. The capacity of cAMP to induce the synthesis of guanylate cyclase-stimulatory CO from smooth muscle cells may represent a novel mechanism by which this nucleotide regulates vascular tone.

L27 ANSWER 4 OF 21 HCAPLUS COPYRIGHT 1999 ACS
AN 1997:310017 HCAPLUS
DN 126:274520
TI Method for measuring **nitrosyl** [Fe(II)]-**hemoglobin** in health and disease
IN Stamler, Jonathan S.
PA Duke University Medical Center, USA; Stamler, Jonathan S.
SO PCT Int. Appl., 18 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9710493	A1	19970320	WO 96-US14660	19960913

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	CA 2232050	AA	19970320	CA 96-2232050	19960913
	AU 9669761	A1	19970401	AU 96-69761	19960913
	AU 693724	B2	19980702		

EP 850408 A1 19980701 EP 96-930855 19960913
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI

PRAI US 95-3801 19950915
US 96-616259 19960315
WO 96-US14660 19960913

AB **Nitrosyl** [Fe(II)]-**Hb** can be detected in biol. samples, e.g., blood, by using a method that involves injection of samples into a photolysis cell, prior to detection of chemiluminescence generated by the reaction between nitric oxide and ozone. This method is useful for monitoring the levels of nitric oxide bioactivity in both normal physiol. states and disease states, such as septic shock, atherosclerosis, **thrombosis**, hyperhomocysteinemia, pulmonary hypertension, malignancy, infections, and central nervous system disorders.

L27 ANSWER 5 OF 21 HCAPLUS COPYRIGHT 1999 ACS
AN 1997:266034 HCAPLUS
DN 126:311807
TI Enhanced modulation of hypotension in endotoxemia by concomitant nitric oxide synthesis inhibition and nitric oxide scavenging
AU Kim, Hae Won; Breiding, Paul; Greenburg, A. Gerson
CS Miriam Hosp., Brown Univ., Providence, RI, 02906, USA
SO Artif. Cells, Blood Substitutes, Immobilization Biotechnol. (1997), 25(1 & 2), 153-162
CODEN: ABSBE4; ISSN: 1073-1199
PB Dekker
DT Journal
LA English
AB Elevated nitric oxide (N) levels appear to be a primary cause of the **sepsis**-related hypotension. We tested a hypothesis that a concomitant NO synthesis inhibition (NOSI) and NO scavenging (NOSC) could effectively modulate this hypotension. Anesthetized SD rats were subjected to endotoxemic shock by i.v. administration of endotoxin (LPS; 10 mg/Kg). Three hours post-LPS, the animals were randomly divided into three groups and infused with 25 mg/Kg of N-amino-L-arginine Me ester (NAME; a No synthesis inhibitor) 130 mg/kg human Hb (a NO scavenger), or a mixt. of both (130 mg Hb/Kg and 25 mg NAME/Kg, N=4). Changes in mean blood pressure (MBP) and erythrocyte and plasma **nitrosyl Hb** (HbNO) levels were followed. The initial MBP increase of the combined treatment was significantly greater than Hb or NAME alone (t-test) and was maintained significantly above the pre-treatment values (paired t-test) 2 h after treatment. All post-LPS erythrocyte samples exhibited the characteristic ESR signals of HbNO at 3.4 kGauss indicating NO formation in endotoxemia. The HbNO signal was also detected in plasma of rats treated with Hb alone or with Hb and NAME indicating the infused Hb reacted with NO. These results indicate that concomitant NOSI and NOSC is more effective than NOSI or NOSC alone in modulating the hypotension of **sepsis** at it combines two distinct but mutually complementary anti-NO mechanisms.

L27 ANSWER 6 OF 21 HCAPLUS COPYRIGHT 1999 ACS
AN 1997:50797 HCAPLUS
DN 126:155746
TI Dynamic aspects of nitric oxide metabolism in health and disease
AU Minamiyama, Yukiko; Inoue, Masayasu

CS Med. Sch., Osaka City Univ., Osaka, 545, Japan
SO Kikan Kagaku Sosetsu (1996), 30, 143-150
CODEN: KKSOEC
PB Nippon Kagakkai
DT Journal; General Review
LA Japanese
AB A review with 22 refs. Nitric oxide (NO) has been implicated to play crit. roles in various physiol. processes including the regulation of vascular resistance, **platelet** aggregation, neurotransmission and immune reaction. However, details of the dynamic aspects of NO metab. remain to be elucidated. The present paper reports the metabolic fate of NO in the circulation and around vascular walls in health and pathol. subjects. To elucidate the fate of NO in the circulation, its adduct, were generated in RBC by NaNO2 and NOC7, NO donors, and the change in cellular levels of **NO, NO-Hb** adducts (**NO-Hb**) and nitrite + nitrate in plasma and tissues were detd. Based on the expts. using ESR (ESR) spectrometer, kinetic aspects of the formation and degrdn. of **NO-Hb** and its metabolites were described. Significant amts. of **NO-Hb** were generated by incubating RBC with either NaNO2 or NOC7. When injected i.v. to normal rats, **NO-Hb** in NaNO2 and NOC7-treated RBC disappeared from the circulation RBC with a half-life of 30 and 16 min, resp. I.v. administration of either NaNO2 or NOC7 increased the blood levels of **NO-Hb**. The metabolic fate of **NO-Hb** differ significantly with NaNO2- and NOC7-treated groups both in vivo and in vitro. **NO-Hb** levels in NOC7-injected rats were significantly lower with animals administered GSH than with control group. These results suggested that the metabolic fate of NO might be affected by the thiol status of animals.

L27 ANSWER 7 OF 21 HCAPLUS COPYRIGHT 1999 ACS
AN 1996:363514 HCAPLUS
DN 125:31906
TI Monoclonal antibody to human cardiac myoglobin, rapid format double antibody immunoassay, and blood analysis for diagnosis of **myocardial** infarction
IN Cardone, Beatrice; Jackowski, George
PA Spectral Diagnostics Inc., Can.
SO PCT Int. Appl., 35 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9610077	A1	19960404	WO 95-IB807	19950928
	W: AU, CA, JP, MX				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	US 5573957	A	19961112	US 94-314044	19940928
	CA 2201153	AA	19960404	CA 95-2201153	19950928
	AU 9534835	A1	19960419	AU 95-34835	19950928
	AU 697522	B2	19981008		
	EP 783569	A1	19970716	EP 95-931369	19950928
	R: DE, FR, GB, SE				
	JP 09511656	T2	19971125	JP 95-511567	19950928

PRAI US 94-314044 19940928
WO 95-IB807 19950928
AB A monoclonal antibody having high affinity to human cardiac myoglobin,

which has undergone a conformational change resulting from the binding of the mol. to another mol. is described. This monoclonal antibody can be used in a rapid format double antibody immunoassay system to identify blood, serum or plasma levels of cardiac myoglobin. Such an immunoassay system can be used for diagnosing and quantifying **myocardial** necrosis and infarction.

L27 ANSWER 8 OF 21 HCAPLUS COPYRIGHT 1999 ACS
AN 1996:355133 HCAPLUS
DN 125:75773
TI Systemic hematologic effects of PEG-rHuMGDF - induced megakaryocyte hyperplasia in mice
AU Ullich, Thomas R.; del Castillo, Juan; Senaldi, Giorgio; Kinstler, Olaf; Yin, Songmei; Kaufman, Stephen; Tarpley, John; Choi, Esther; Kirley, Theresa; et al.
CS Amgen Inc., Thousand Oaks, CA, 91320, USA
SO Blood (1996), 87(12), 5006-5015
CODEN: BLOOAW; ISSN: 0006-4971
DT Journal
LA English
AB Peg-rHuMGDF injected daily in normal mice causes a rapid dose-dependent increase in megakaryocytes and **platelets**. At the same time that **platelet** nos. are increased, the mean **platelet** vol. (MPV) and **platelet** distribution width (PDW) can be either decreased, normal, or increased depending on the dose and time after administration. Thus, PEG-rHuMGDF at a low dose causes decreases in MPV and PDW, MGDF at an intermediate dose causes an initial increase followed by a decrease in MPV and PDW, and PEG-rHuMGDF at higher doses causes an increase in MPV and PDW followed by a gradual normalization of these **platelet** induces. In addn. to the expected **thrombocytosis** after 7 to 10 days of daily injection of high doses of PEG-rHuMGDF, a transient decrease in peripheral red blood cell **nos**. and **Hb** is noted accompanied in the bone marrow by megakaryocytic hyperplasia, myeloid hyperplasia, erythroid and lymphoid hypoplasia, and deposition of a fine network of reticulin fibers. Splenomegaly, an increase in splenic megakaryocytes, and extramedullary hematopoiesis accompany the hematol. changes in the peripheral blood and marrow to complete a spectrum of pathol. features similar to those reported in patients with myelofibrosis and megakaryocyte hyperplasia. However, all the PEG-rHuMGDF-initiated hematopathol. including the increase in marrow reticulin is completely and rapidly reversible upon the cessation of administration of PEG-rHuMGDF. Thus, transient hyperplastic proliferation of megakaryocytes does not cause irreversible tissue injury. Furthermore, PEG-rHuMGDF completely ameliorates carboplatin-induced **thrombocytopenia** at a low-dose that does not cause the hematopathol. assocd. with myelofibrosis.

L27 ANSWER 9 OF 21 HCAPLUS COPYRIGHT 1999 ACS
AN 1996:324500 HCAPLUS
DN 125:7139
TI Dynamic aspects and role of nitric oxide in endotoxin-induced liver injury
AU Takemura, S.; Minamiyama, Y.; Kinoshita, H.; Inoue, M.
CS Medical School, Osaka City University, Abeno, 545, Japan
SO Portland Press Proc. (1996), 10(Biology of Nitric Oxide Part 5), 278
CODEN: POPPEF
DT Journal

LA English
AB The dynamic aspects of the induction of NO synthase (NOS) in various tissues, formation of **NO-Hb** adducts in the circulating RBCs, nitrosyl heme-iron complexes in the liver, and plasma nitrite + nitrate (NOx) in endotoxemic rats are presented. The crit. role of NO in the pathogenesis of endotoxemia is also discussed.

L27 ANSWER 10 OF 21 HCAPLUS COPYRIGHT 1999 ACS
AN 1996:94526 HCAPLUS
DN 124:193838
TI Nitric oxide-donating properties of mesoionic 3-aryl substituted oxatriazole-5-imine derivatives
AU Kankaanranta, H.; Rydell, E.; Petersson, A.-S.; Holm, P.; Moilanen, E.; Corell, T.; Karup, G.; Vuorinen, P.; Pedersen, S. B.; et al.
CS Medical School, Univ. Tampere, Tampere, FIN-33101, Finland
SO Br. J. Pharmacol. (1996), 117(3), 401-6
CODEN: BJPCBM; ISSN: 0007-1188
DT Journal
LA English
AB The nitric oxide (NO)-releasing properties of two new mesoionic 3-aryl substituted oxatriazole-5-imine derivs. (GEA 3162 and GEA 3175) were characterized and compared with the known NO-donors 3-morpholino-sydnonimine (SIN-1) and S-nitroso-N-acetylpenicillamine (SNAP). GEA 3162, GEA 1375, SIN-1 and SNAP inhibited ADP-induced **platelet** aggregation (IC50 values 0.18, 0.39, 3.73 and 2.12 .mu.M, resp.). All four compds. induced a dose-dependent and more than 4 fold increase in cGMP in **platelets**. The increase in cGMP concn. was potentiated more than 1.5 fold by a phosphodiesterase inhibitor, zaprinast (10 .mu.M) and inhibited 38-97% by oxyHb (10-45 .mu.M). All of the four compds. studied converted oxyHb to metHb and formed a paramagnetic **NO-Hb** complex. All but GEA 3175 formed nitrite and nitrate in phosphate buffer. During a 40 min incubation, GEA 3162, SIN-1 and SNAP (100 .mu.M) produced 50-70 .mu.M NO2- + NO3- as detd. by high performance liq. chromatog. The release of NO and NO2 by GEA 3175 was increased 140 fold in the presence of human plasma (0.14 and 19.7 ppb in the absence and presence of 1% human plasma, resp.) as analyzed by ozone chemiluminescence. The results suggest that the mesoionic 3-aryl substituted oxatriazole-5-imine derivs. GEA 3162 and GEA 3175 as well as SIN-1 and SNAP release nitric oxide.

L27 ANSWER 11 OF 21 HCAPLUS COPYRIGHT 1999 ACS
AN 1995:670883 HCAPLUS
DN 123:218002
TI **Nitrosyl hemoglobin** formation in-vivo after intravenous administration of a hemoglobin-based oxygen carrier in endotoxemic rats
AU Greenburg, A. G.; Kim, H. W.
CS Miriam Hospital, Brown University, Providence, RI, 02906, USA
SO Artif. Cells, Blood Substitutes, Immobilization Biotechnol. (1995), 23(3), 271-6
CODEN: ABSBE4; ISSN: 1073-1199
DT Journal
LA English
AB Interaction of Hb-based oxygen carriers (HBOCs) with nitric oxide (NO) of endothelium or macrophage origin has been implicated in the obsd. vasoconstriction after HBOC infusion. Definitive evidence supporting this

interaction, in-vivo, has not been reported. The authors report here a confirmed in-vivo formation of **nitrosyl Hb** (HbNO), a product of Hb and NO reaction, in endotoxemic rats following i.v. administration of a HBOC. Male Sprague-Dawley rats were rendered endotoxemic by i.v. injection of lipopolysaccharide (LPS, 10 mg/kg), and five hours later HBOC (1.2 g Hb/kg) was infused. Changes in blood pressure (BP) and HbNO levels were followed. HBOC infusion immediately reversed the hypotension of endotoxemia. In addn., HBOC infusion caused plasma HbNO formation detd. by ESR spectroscopy. This is direct evidence of NO reaction with infused Hb. In conclusion, HBOC interacts in-vivo with NO directly in a model with increased NO. Whether this effect is present at basal levels of NO requires exploration.

L27 ANSWER 12 OF 21 HCAPLUS
AN 1994:505717 HCAPLUS
DN 121:105717
TI Arterial smooth muscle cells express nitric oxide synthase in response to endothelial injury
AU Hansson, Goran K.; Geng, Yong-jian; Holm, Jan; Haardhammar, Peter; Wennmalm, Aake; Jennische, Eva
CS Dep. Clin. Chem., Gothenburg Univ., Gothenburg, S-413 45, Swed.
SO J. Exp. Med. (1994), 180(2), 733-8
CODEN: JEMEAV; ISSN: 0022-1007
DT Journal
LA English
AB Endothelial cells regulate vascular tone by secreting paracrine mediators that control the contractility of arterial smooth muscle cells. Nitric oxide (NO) is an important vasodilating agent that is generated from L-arginine by the enzyme nitric oxide synthase (NOS), which is expressed constitutively by the endothelium. NO also inhibits **platelet** aggregation, contributing to the antithrombotic properties of the endothelial surface. It would therefore be expected that loss of the endothelium during arterial injury would lead to vasospasm and **thrombosis** but instead, the neointima formed after injury has a nonthrombogenic surface and a maintained vascular patency. The authors report here that arterial smooth muscle cells in the neointima formed after a deendothelializing balloon injury to the rat carotid artery express the cytokine-inducible isoform of NOS. Expression was detectable by reverse transcription-polymerase chain reaction from day 1-14 after injury and in situ hybridization showed expression of NOS mRNA by neointimal smooth muscle cells, particularly at the surface of the lesion.
This was assocd. with systemically detectable NO prodn. as revealed by ESR spectroscopic anal. of **nitrosylated** red cell **Hb**.
Local NO prodn. by intimal smooth muscle cells after endothelial injury could represent an important mechanism for the maintenance of arterial patency and nonthrombogenicity in the injured artery.

L27 ANSWER 13 OF 21 HCAPLUS
AN 1994:154683 HCAPLUS
DN 120:154683
TI Role of nitric oxide in eicosanoid synthesis and uterine motility in estrogen-treated rat uteri
AU Franchi, Ana Maria; Chaud, Marcela; Rettori, Valeria; Suburo, Angela; McCann, Samuel M.; Gimeno, Martha
CS Cent. Estud. Farmacol. Bot., Consejo Nac. Invest. Cient. Tec., Buenos Aires, 1414, Argent.
SO Proc. Natl. Acad. Sci. U. S. A. (1994), 91(2), 539-43

CODEN: PNASA6; ISSN: 0027-8424
DT Journal
LA English
AB The role of NO in controlling contraction of uterine smooth muscle was investigated in rats. The authors began by detg. whether NO was involved in prodn. of arachidonic acid metabolites in the uterus. Uteri were removed from female rats that had been treated with 17.beta.-estradiol. Control animals were similarly injected with diluent. Tissues were incubated in vitro in the presence of [14C]arachidonic acid for 60 min. Synthesis of prostaglandins (PGs) and **thromboxane** B2 (TXB2) was markedly stimulated by sodium nitroprusside (NP), the releaser of NO. The effect was greatest on TXB2; there were no significant differences in increases of different PGs. The response to NP was completely prevented by Hb, a scavenger of NO. The inhibitor of NO synthase (Nitric Oxide Synthase), NG-monomethyl-L-arginine (NMMA), significantly decreased synthesis of PGE2, but not TXB2. There was a much lesser effect on products of lipoxygenase, such that only 5-hydroxy-5,8,11,14-eicosatetraenoic acid (5-HETE) synthesis was increased by NP, an effect that was blocked by Hb; there was no effect of NMMA of Hb on basal prodn. of 5-HETE. Thus, NO stimulates release of the various prostanoids and 5-HETE; blockage of NOS blocked only PGE2 release, whereas Hb to scavenge the NO released also blocked synthesis of 6-keto-PGF1.alpha., PGE2, and PGF2.alpha., indicating that basal NO release is involved in synthesis of all these PGs, esp. PGE2. To det. the role of these prostanoids and NO in control of spontaneous in vitro uterine contractility in the estrogen-treated uterus, the effect of blocking NOS with NMMA and of scavenging NO produced by Hb on the time course of spontaneous uterine contractility was studied. Surprisingly, blockade of NOS or removal of **NO** by **Hb** prevented the spontaneous decline in uterine motility that occurs over 40 min of incubation. When the motility had declined to minimal levels, the effect of increased NO provided by NP was evaluated; apparently by stimulating the release of prostanoids, a rapid increase in motility that persisted for 10 min was produced. This effect was completely blocked by Hb. The action of NP was also blocked by indomethacin, indicating that it was acting via release of PGs. Apparently, when motility is low, activation of PG synthesis by NO to activate the cyclooxygenase enzyme causes a rapid induction of contractions, whereas, when motility is declining, NO acts primarily via guanylate cyclase to activate cGMP release; the action of the prostanoids released at this time is in some manner blocked.

L27 ANSWER 14 OF 21 HCAPLUS
AN 1993:425697 HCAPLUS
DN 119:25697
TI Electron paramagnetic resonance detection of iron-nitrosyl complex formation in cytokine-treated rat hepatocytes and in blood and liver during **sepsis**
AU Lancaster, J. R., Jr.; Stadler, J.; Billiar, T. R.; Bergonia, H. A.; Kim, Y. M.; Piette, L. H.; Simmons, R. L.
CS Dep. Chem. Biochem., Utah State Univ., Logan, UT, 84322-0300, USA
SO Biol. Nitric Oxide, Proc. Int. Meet., 2nd (1992), Meeting Date 1991, Volume 2, 76-80. Editor(s): Moncada, Salvador. Publisher: Portland Press, London, UK.
CODEN: 59AFA7
DT Conference
LA English

AB This study demonstrated the usefulness of ESR (EPR) in studying the appearance of iron-nitrosyl complexes in blood and hepatocytes in the host response to infection.

L27 ANSWER 15 OF 21 HCAPLUS COPYRIGHT 1999 ACS
AN 1991:556199 HCAPLUS
DN 115:156199
TI Nitric oxide hemoglobin in mice and rats in endotoxic shock
AU Wang, Qizhi; Jacobs, Judith; DeLeo, Joyce; Kruszyna, Harriet; Kruszyna, Robert; Smith, Roger; Wilcox, Dean
CS Dep. Pharmacol. Toxicol., Dartmouth Med. Sch., Hanover, NH, USA
SO Life Sci. (1991), 49(11), PL55-PL60
CODEN: LIFSAK; ISSN: 0024-3205
DT Journal
LA English
AB Mice given i.p. bacterial endotoxin (LPS) at 10 mg/kg showed a statistically significant decrease in plasma glucose and an increase in hematocrit at 2 h after injection. Glucose was still decreased at 4 h, but the hematocrit had returned to control values. **Nitrosylated Hb** (HbNO) was detected at 3, but not at 2 h. By 4 h it had increased 5-fold. When N-monomethylarginine (NMMA) at 100 mg/kg, i.p. was given 2 h after LPS in mice, the HbNO concn. at 4 h was reduced, but the hypoglycemia was worsened because NMMA itself produced hypoglycemia. Rats given i.v. LPS, 20 mg/kg, showed a fleeting, transient rise in mean arterial pressure (MAP) lasting only a few min. Thereafter, the MAP tended to drift slowly downward over 4 h, but when the MAP at 30 min intervals was compared to the pre-LPS MAP, there were no differences. Plasma glucose in unanesthetized rats was elevated at 1 h, back to control at 2 h, and decreased at 3 h. HbNO was detected as early as 1 h after injection. By 2 h the HbNO concns. exceeded the highest levels found in mice, and they were still increasing as late as 5 h after injection. Unanesthetized rats showed toxic signs and 3/12 rats died with 4 h of LPS administration. These results are consistent with a model for endotoxic shock in which LPS stimulates an inducible pathway for NO synthesis.

L27 ANSWER 16 OF 21 HCAPLUS COPYRIGHT 1999 ACS
AN 1991:425556 HCAPLUS
DN 115:25556
TI Monoclonal antibody specific to ventricular myosin light chain 1 (VLC1) used in enzyme immunoassay for the light chain detection in cardiac patients
IN Sikorska, Hanna; Hebert, Manon; Kowalik, Maria
PA Rougier Inc., Can.
SO PCT Int. Appl., 59 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9015329	A1	19901213	WO 90-CA177	19900531
	W: CA				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, IT, LU, NL, SE				

PRAI US 89-360141 19890601
US 90-530836 19900530

AB A competitive method of measuring human ventricular myosin light chain (HVLC) in cardiac patients comprises incubating .gtoreq.1 monoclonal or polyclonal anti-HVLCs antibody, an enzyme, a VLCs antigen and an unknown amt. of HVLCs analyte present in patient's serum. The anti-HVLCs antibody or the VLCs antigen, is directly or indirectly detected by means of enzyme-bound label, whereby the amt. of HVLCs analyte, when initially present in patient's serum, is detd. by comparing the extent to which the said VLCs antigen is bound to the said anti-HVLCs antibody with a calibration curve obtained from a known amt. of said antigen. The anti-HVLCs antibody or the VLCs antigen is solid-phase bound. The anti-HVLCs monoclonal antibody has specificity to .gtoreq.1 of HVLC1 and HVLC2. There is prepd. a monoclonal antibody which specifically binds to VLC1 and which is produced by the hybridoma cell line having the ATCC accession **no. HB** 10471. For competitive EIA, test VLC, and anti-VLC, antibody in a VLC1-sensitized polystyrene microtiter plate were incubated, followed by incubation with horseradish peroxidase-conjugated goat anti-mouse IgG at 37.degree.. After washing, the bound enzyme activity was measured colorimetrically for the VLC1 detn.
Serum VLC1 levels were elevated in patients with **myocardial** infarction. Kits for the competitive immunoassay also are claimed.

L27 ANSWER 17 OF 21 HCAPLUS COPYRIGHT 1999 ACS
AN 1991:415025 HCAPLUS
DN 115:15025
TI Hematological effects in fishes from complex polluted waters of Visakhapatnam Harbor
AU Rao, D. Panduranga; Bhaskar, B. Ram; Rao, K. Srinivasa; Prasad, Y. V. K. Durga; Rao, N. Someswara; Rao, T. N. V. Venkateswara
CS Dep. Zool., Andhra Univ., Visakhapatnam, 530 003, India
SO Mar. Environ. Res. (1990), 30(3), 217-31
CODEN: MERSDW; ISSN: 0141-1136
DT Journal
LA English
AB Five species of fish from 2 polluted stations in Visakhapatnam harbor waters (in India) were compared hematol. with the same species from 2 control stations-one at Gostani estuary of Bhimilipatnam and another in the inshore waters of Visakhapatnam coast. All species from polluted waters showed significantly higher mean cell vol. (MCV), leukocyte **nos.**, hematocrit, **Hb** and **thrombocyte** percentage; and significantly higher MCV, leukocyte nos. and lymphocyte percentage, compared with the controls. The obsd. adverse hematol. characteristics of fish from polluted waters were probably due more to synergistic effects of the toxicants (Pb, Cd, Cu, Fe, Zn, Mn and oil and grease) rather than to the effects of each toxicant sep.

L27 ANSWER 18 OF 21 HCAPLUS COPYRIGHT 1999 ACS
AN 1990:132102 HCAPLUS
DN 112:132102
TI Effect of cyanide on the reaction of nitroprusside with hemoglobin: relevance to cyanide interference with the biological activity of nitroprusside
AU Wilcox, Dean E.; Kruszyna, Harriet; Kruszyna, Robert; Smith, Roger P.
CS Dep. Chem., Dartmouth Coll., Hanover, NH, 03755, USA
SO Chem. Res. Toxicol. (1990), 3(1), 71-6
CODEN: CRTOEC; ISSN: 0893-228X
DT Journal
LA English

OS CJACS
AB The reaction of sodium nitroprusside (SNP) with deoxyHb (Hb) results in 2 distinct EPR-detectable species, the one-electron-reduced nitroprusside ion [(CN)5FeNO]3- and nitrosylHb (HbNO). In the presence of excess cyanide (CN-), only the signal for [(CN)5FeNO]3- is obsd. Thus, while free CN- does not interfere with Hb redn. of SNP, it prevents transfer of the NO moiety to Hb. Electrolytic redn. of SNP under identical conditions, however, leads to the formation of [(CN)5FeNO]3- and a small amt. of [(CN)4FeNO]2- resulting from loss of the CN- trans to the NO. Excess free CN- shifts the equil. between these 2 species toward [(CN)5FeNO]3-, thereby reducing the concn. of [(CN)4FeNO]2-. Thus, [(CN)4FeNO]2- appears to be responsible for the transfer of **NO** to **Hb**. Consistent with this mechanism, both [(CN)5FeNO]3- and [(CN)4FeNO]2- are obsd. when SNP is added to erythrocyte lyzates. Under these conditions HbNO is formed more rapidly due to the higher concn. of the latter species with the labile NO. This observation suggests that red blood cell constituents capable of binding CN- shift the equil. between the reduced SNP ions toward [(CN)4FeNO]2-. In the reaction of GSH with SNP, [(CN)5FeNO]3- is formed as well as low concns. of an EPR-detectable GSH-SNP adduct. Excess free CN- introduces a lag in the appearance of these signals, suggesting that GSH mediates SNP redn. by a different mechanism from that of Hb, although it too is inhibited by CN-. The CN-stabilization of [(CN)5FeNO]3-, the reduced SNP species lacking a labile NO moiety, probably accounts for the ability of CN- to block or reverse the biol. effects of SNP on aortic strips and human blood **platelets**. This chem. interaction appears to meet many of the criteria for competitive antagonism. By comparison, the vasodilator 3-morpholinosydnoneimine, which is a metabolite of molsidomine and which has an alkyl cyano and an alkyl nitroxide groups, releases NO by an entirely different mechanism since free CN- has no effect on its biol. activity.

L27 ANSWER 19 OF 21 HCAPLUS COPYRIGHT 1999 ACS
AN 1986:143490 HCAPLUS
DN 104:143490
TI Effect of hydrazine on certain hematological indexes of carp
AU Tishinova-Nanova, V.
CS Biol. Fak., Su Kl. Okhridski, Sofia, 1421, Bulg.
SO Khidrobiologiya (1985), 26, 41-8
CODEN: KHIDD9; ISSN: 0324-0924
DT Journal
LA Bulgarian
AB In carp larva (.apprx.11 g body wt.) exposed to 0.1-10 mg N2H4/L for 24 h at 18.degree., the no. of erythrocytes in blood was above normal. Hb concn. in blood was below normal at 5 mg NH4/L and above normal at 10 mg NH4/L. Hematocrit value and neutrophil no. were above normal and total lymphocyte no. below normal at 5-10 mg N2H4/L. Leukocyte no. and **thrombocyte** no. were above normal at 0.1-1.0 and 0.1-10.0 mg N2H4/L, resp. The increases in erythrocyte **no.** and **Hb** concn. may be compensatory responses to O insufficiency. The increased no. of **thrombocytes** also indicates asphyxia.

L27 ANSWER 20 OF 21 HCAPLUS COPYRIGHT 1999 ACS
AN 1981:44378 HCAPLUS
DN 94:44378
TI Myoglobin and cytochrome oxidase in the **myocardium** of the developing chick
AU Meszaros, Karoly; Chance, Britton; Holtzer, Howard

CS Sch. Med., Univ. Pennsylvania, Philadelphia, PA, USA
SO J. Mol. Cell. Cardiol. (1980), 12(10), 965-75
CODEN: JMCDAY; ISSN: 0022-2828
DT Journal
LA English
AB **Myocardial** tissue of chick embryos and developing chickens 3-30 days of age was investigated by spectrophotometry. Spectral and kinetic evidence showed that **no Hb** was present in the **myocardial** tissue prepns. Difference spectra of anoxic vs. oxygenated heart tissue of 3- and 4-day-old embryos demonstrated the oxidn.-redn. changes of cytochromes only. At variance with the results of previous studies, myoglobin was first detected at an age of 5 days. At later developmental stages myoglobin dominated the spectrum. Therefore, to demonstrate the presence of cytochromes, myoglobin was transformed into derivs. incapable of O binding by treatment of the tissue with NO2- or EtOOH. The molar ratio of myoglobin to cytochrome oxidase increased rapidly from 5 to 14 days of age; thereafter a slow decrease was obsd.

L27 ANSWER 21 OF 21 HCAPLUS COPYRIGHT 1999 ACS
AN 1974:534020 HCAPLUS
DN 81:134020
TI Hemostatic and homeostatic changes following massive autotransfusion in the dog
AU Rakower, S. R.; Worth, M. H., Jr.; Berman, I.; Lackner, H.
CS Bellevue Med. Cent., New York Univ., New York, N. Y., USA
SO J. Trauma (1974), 14(7), 594-604
CODEN: JOTRA5
DT Journal
LA English
AB The effects of massive autotransfusion (blood reinfusion) in exptl. dogs were examd. and compared with the known consequences of conventional blood transfusion. A controlled vascular injury model was used to simulate a clin. massive ongoing blood loss without gastrointestinal tract contamination. A consistent fall in blood pressure, pH, arterial and venous O concn., hematocrit, and **platelet** counts was obsd. The primary factor responsible for these changes apparently was the blood-tissue contact in the extravascular compartment prior to reinfusion. However, mech. factors inherent in the process of reinfusion, e.g., the air-blood interface, undoubtedly had some effect in this exptl. model. All animals demonstrated some degree of hemolysis following 2 blood vols. autotransfusion, as well as decreased plasma fibrinogen levels and increased partial **thromboplastin** times. The prothrombin and **thrombin** times were unchanged, and there was **no hemoglobinuria**. Thus, addnl. blood and **platelets** as well as plasma vol. expansion (extenders) may be required during surgery to prevent the clin. posttraumatic pulmonary insufficiency syndrome.

=> D L34 1-4 BIB ABS

L34 ANSWER 1 OF 4 MEDLINE DUPLICATE 1
AN 1998122360 MEDLINE
DN 98122360
TI Cell-free and erythrocytic S-nitrosohemoglobin inhibits human **platelet** aggregation.
AU Pawloski J R; Swaminathan R V; Stamler J S
CS Department of Medicine, Duke University Medical Center, Durham, NC 27710, USA.
SO CIRCULATION, (1998 Jan 27) 97 (3) 263-7.
Journal code: DAW. ISSN: 0009-7322.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 199804
AB BACKGROUND: Nitric oxide (NO) and related molecules are thought to inhibit human **platelet** aggregation by raising levels of cGMP. METHODS AND RESULTS: Both oxidative stress (reactive oxygen species) and hemoglobin (Hb) seem to oppose NO effects. A major fraction of NO in the blood is bound to thiols of **Hb**, forming S-nitrosohemoglobin (**SNO-Hb**), which releases the NO group on deoxygenation in the microcirculation. Here we show that (1) both cell-free and intraerythrocytic **SNO-Hb** (**SNO**-RBC) inhibit **platelet** aggregation, (2) the oxidation state of the hemes in **Hb** influences the response--**SNO**-metHb (which is functionally similar to SNO-deoxyHb) has greater **platelet** inhibitory effects than SNO-oxyHb, and (3) the mechanism of **platelet** inhibition by **SNO-Hb** is cGMP independent. CONCLUSIONS: We suggest that the RBC has evolved a means to counteract **platelet** activation in small vessels and the proaggregatory effects of oxidative stress by forming **SNO-Hb**.

L34 ANSWER 2 OF 4 MEDLINE DUPLICATE 2
AN 94321932 MEDLINE
DN 94321932
TI Arterial smooth muscle cells express nitric oxide synthase in response to endothelial injury.
AU Hansson G K; Geng Y J; Holm J; Hardhammar P; Wennmalm A; Jennische E
CS Department of Clinical Chemistry, Gothenburg University, Sweden..
SO JOURNAL OF EXPERIMENTAL MEDICINE, (1994 Aug 1) 180 (2) 733-8.
Journal code: I2V. ISSN: 0022-1007.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199411
AB Endothelial cells regulate vascular tone by secreting paracrine mediators that control the contractility of arterial smooth muscle cells. Nitric oxide (NO) is an important vasodilating agent that is generated from L-arginine by the enzyme nitric oxide synthase (NOS), which is expressed constitutively by the endothelium. NO also inhibits **platelet** aggregation, contributing to the antithrombotic properties of the endothelial surface. It would therefore be expected that loss of the

endothelium during arterial injury would lead to vasospasm and **thrombosis** but instead, the neointima formed after injury has a nonthrombogenic surface and a maintained vascular patency. We report here that arterial smooth muscle cells in the neointima formed after a deendothelializing balloon injury to the rat carotid artery express the cytokine-inducible isoform of NOS. Expression was detectable by reverse transcription-polymerase chain reaction from day 1-14 after injury and in situ hybridization showed expression of NOS mRNA by neointimal smooth muscle cells, particularly at the surface of the lesion. This was associated with systemically detectable NO production as revealed by electron paramagnetic resonance spectroscopic analysis of **nitrosylated** red cell **hemoglobin**. Local NO production by intimal smooth muscle cells after endothelial injury could represent an important mechanism for the maintenance of arterial patency and nonthrombogenicity in the injured artery.

L34 ANSWER 3 OF 4 DRUGU COPYRIGHT 1999 DERWENT INFORMATION LTD
AN 99-03071 DRUGU P
TI Possibility of S-nitrosohemoglobin as a new cardioprotective agent.
AU Sakuma I; Nakai K; Togashi H; Fujii S; Yoskioka M; Sato H; Kitabatake A
CS Univ.Hokkaido; Univ.Tohoku
LO Sapporo; Sendai, Jap.
SO J.Mol.Cell.Cardiol. (30, No. 11, 317, 1998)
CODEN: JMCDAY ISSN: 0022-2828
AV Department of Cardiovascular Medicine, Hokkaido University, Sapporo, Japan.
LA English
DT Journal
FA AB; LA; CT
FS Literature
AN 99-03071 DRUGU P
AB The potential cardioprotective effects of i.v. S-nitrosohemoglobin (**SNO-Hb**), as compared to cell free **hemoglobin** (Hb), used as an artificial red blood cell substitute were investigated in-vivo in rats. The results demonstrate that **SNO-Hb** exhibits properties desirable for an artificial red blood cell substitute and may be used as a cardioprotective agent that supplies oxygen and NO and quenches excessive NO in the heart. (conference abstract: XV Meeting of the Japanese Section of the International Society for Heart Research, Tokyo, Japan, 1998).
ABEX The i.v. administration of Hb (125 mg/kg) to Wistar rats resulted in a 28 mmHg increase in B.P. I.v. administration of **SNO-Hb** (125 mg/kg) decreased B.P. by 9 mmHg. Neither **Hb** nor **SNO-Hb** modified **platelet** aggregation. **SNO-Hb**, nut not **Hb**, induced an increase in the plasma and brain levels of NO2-/NO3-. (SK)

L34 ANSWER 4 OF 4 SCISEARCH COPYRIGHT 1999 ISI (R)
AN 93:641243 SCISEARCH
GA The Genuine Article (R) Number: MC066
TI MODULATION OF HUMAN T-CELL RESPONSES BY NITRIC-OXIDE AND ITS DERIVATIVE, S-NITROSOGLUTATHIONE
AU MERRYMAN P F (Reprint); CLANCY R M; HE X Y; ABRAMSON S B
CS HOSP JOINT DIS & MED CTR, DEPT RHEUMATOL & MOLEC MED, NEW YORK, NY, 10003;
NYU, SCH MED, DEPT MED, DIV RHEUMATOL, NEW YORK, NY, 10003
CYA USA

SO ARTHRITIS AND RHEUMATISM, (OCT 1993) Vol. 36, No. 10, pp. 1414-1422.
ISSN: 0004-3591.
DT Article; Journal
FS LIFE; CLIN
LA ENGLISH
REC Reference Count: 42
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Objective. To examine the effects of nitric oxide (NO) and its more stable derivative, S-nitrosoglutathione (SNO-GSH), on the response of activated T lymphocytes.

Methods. The effects of NO and SNO-GSH on DNA synthesis, interleukin-2 (IL-2) production, IL-2 receptor expression, and cGMP accumulation were determined in phytohemagglutinin-activated peripheral blood mononuclear cells (PBMC) and spleen T cells.

Results. Nitric oxide (half-life [T1/2] < 15 seconds) did not inhibit T

cell proliferation. However, the derivative SNO-GSH (25 muM) (T1/2 >2 hours) inhibited DNA synthesis by a mean +/- SD of 65 +/- 19.6% (P < 0.001) in PBMC and 75 +/- 15% (P < 0.001) in spleen cells. Macrophage depletion of PBMC did not abrogate the inhibition. SNO-GSH had no effect on IL-2 production or IL-2 receptor expression. NO (25 muM) increased the cGMP content of PBMC (0.65 +/- 0.15 pmoles/10(6) cells; P < 0.04), as did SNO-GSH (25 muM) in both PBMC (3.8 +/- 1; P < 0.001) and spleen T cells (5.2 +/- 1.2; P < 0.001). Methylene blue and **hemoglobin,** which are NO inhibitors, inhibited **SNO**-GSH-induced cGMP accumulation (P < 0.001).

Conclusion. SNO-GSH inhibits T cell DNA synthesis independently of IL-2

production and in association with cGMP accumulation via a NO-dependent mechanism. We suggest that NO and its S-nitrosothiol derivatives may act as endogenous inhibitors of T cell-mediated inflammation.

=> D BIB ABS

L35 ANSWER 1 OF 20 MEDLINE DUPLICATE 1
AN 1998161299 MEDLINE
DN 98161299
TI Inactivation of the cardiac ryanodine receptor calcium release channel by **nitric oxide.**
AU Zahradnikova A; Minarovic I; Venema R C; Meszaros L G
CS Department of Physiology & Endocrinology, Medical College of Georgia, Augusta 30912, USA.
SO CELL CALCIUM, (1997 Dec) 22 (6) 447-54.
Journal code: CQE. ISSN: 0143-4160.
CY SCOTLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199806
EW 19980604
AB We have recently reported [Meszaros L.G., Minarovic I., Zahradnikova A. Inhibition of the skeletal muscle ryanodine receptor calcium release channel by **nitric oxide.** FEBS Lett 1996; 380: 49-52] that **nitric oxide** (NO) reduces the activity of the skeletal muscle ryanodine receptor Ca2+ release channel (RyRC), a principal component of the excitation-contraction coupling machinery in striated muscles. Since (i) as shown here, we have obtained evidence which indicates that the NO synthase (eNOS) of cardiac muscle origin co-purified with RyRC-containing sarcoplasmic reticulum (SR) fractions; and (ii) the effects of NO donors on the release channel, as well as on cardiac function, appear somewhat contradictory, we have made an attempt to investigate the response of the cardiac RyRC to NO that is generated in situ from L-arginine in the NOS reaction. We found that L-arginine-derived NO inactivates Ca2+ release from cardiac SR and reduces the steady-state activity (i.e. open probability) of single RyRCs fused into a planar lipid bilayer. This reduction was prevented by NOS inhibitors and the **NO** quencher **hemoglobin** and was reversed by 2-mercaptoethanol. We thus conclude that: (i) in isolated SR preparations, it is possible to assess the effects of NO that is generated from L-arginine in the NOS reaction; and (ii) cardiac RyRc responds to NO in a manner which is identical to that we have previously found with the skeletal channel. These findings suggest that the direct modulation of the RyRC by NO is a signaling mechanism which likely participates in earlier demonstrated NO-induced **myocardial** contractility changes.

=> D BIB ABS 2-20

L35 ANSWER 2 OF 20 MEDLINE DUPLICATE 2
AN 97392988 MEDLINE
DN 97392988
TI cAMP induces heme oxygenase-1 gene expression and carbon monoxide production in vascular smooth muscle.
AU Durante W; Christodoulides N; Cheng K; Peyton K J; Sunahara R K; Schafer A I

CS Houston Veterans Affairs Medical Center, Texas, USA.
NC HL-36045 (NHLBI)
SO AMERICAN JOURNAL OF PHYSIOLOGY, (1997 Jul) 273 (1 Pt 2) H317-23.
Journal code: 3U8. ISSN: 0002-9513.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199711
AB Recent studies indicate that vascular smooth muscle cells generate carbon monoxide (CO) via the action of heme oxygenase (HO). Because adenosine 3',5'-cyclic monophosphate (cAMP) is an important intracellular signaling molecule in the regulation of vascular cell function, we examined whether this second messenger modulates the expression of HO and the production of CO by rat aortic smooth muscle cells. Treatment of smooth muscle cells with the membrane-permeable cAMP derivative dibutyryl cAMP or with compounds that increase intracellular cAMP levels (isoproterenol and forskolin) resulted in a concentration- and time-dependent increase in the levels of HO-1 mRNA and protein, whereas the expression of HO-2 remained unchanged. Both actinomycin D and cycloheximide blocked the basal expression of HO-1 mRNA and protein and prevented the cAMP-mediated induction of HO-1. Incubation of **platelets** with cAMP-treated smooth muscle cells resulted in a significant increase in **platelet** cGMP concentration that was partially reversed by treatment of smooth muscle cells with the **nitric oxide** synthase inhibitor NG-monomethyl-L-arginine or the HO blocker zinc protoporphyrin-IX. However, the combined addition of these two inhibitors to cAMP-treated smooth muscle cells or the addition of the CO and **NO** scavenger **hemoglobin** to **platelets** completely blocked the stimulatory effect on **platelet** cGMP levels. These results demonstrate that cAMP induces the expression of the HO-1 gene and stimulates the formation of CO and NO in vascular smooth muscle cells. The capacity of cAMP to induce the synthesis of guanylate cyclase-stimulatory CO from smooth muscle cells may represent a novel mechanism by which this nucleotide regulates vascular tone.

L35 ANSWER 3 OF 20 MEDLINE DUPLICATE 3
AN 97036948 MEDLINE
DN 97036948
TI The effect of ischaemia on endothelium-dependent vasodilatation and adrenoceptor-mediated vasoconstriction in rat isolated hearts.
AU Pannangpetch P; Woodman O L
CS Department of Pharmacology, University of Melbourne, Parkville, Victoria, Australia.
SO BRITISH JOURNAL OF PHARMACOLOGY, (1996 Mar) 117 (6) 1047-52.
Journal code: B00. ISSN: 0007-1188.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199702
EW 19970204
AB 1. The aim of this study was to investigate whether global ischaemia and reperfusion in rat isolated hearts affects endothelium-dependent vasodilatation and adrenoceptor-mediated vasoconstriction. In addition, it

was first determined whether inhibition of the actions of **nitric oxide** (NO) influenced the responses to alpha-adrenoceptor agonists in the rat coronary vasculature. 2. In rat isolated, Langendorff perfused hearts, inhibition of **NO** with **haemoglobin** (Hb, 6 microM) significantly inhibited the vasodilator responses to the endothelium-dependent vasodilators, acetylcholine (ACh, 3-100 pmol), carbachol (CCh, 10-300 pmol), bradykinin (Bk, 1-30 pmol) and histamine (0.3-10 nmol) but did not affect responses to the endothelium-independent vasodilator, sodium nitroprusside (SNP, 0.01-1 nmol). 3. Inhibition of the action of **NO** by **Hb** significantly enhanced the vasoconstrictor response to the non-selective alpha-adrenoceptor agonist, noradrenaline (NA, 0.1-10 nmol) and the alpha 2-adrenoceptor agonist, B-HT 920 (0.001-1 mumol) but had no effect on the vascular response to the alpha 1-adrenoceptor agonist, methoxamine (MTX, 10-300 nmol). 4. In the perfused hearts ischaemia, induced by 30 min perfusion at 5% of the normal rate of flow, followed by 15 min of reperfusion (ischaemia/reperfusion) selectively impaired the vasodilator responses to ACh and CCh which act by muscarinic receptor stimulation but did not affect responses to the other endothelium-dependent vasodilators Bk and histamine or to the endothelium-independent dilator SNP. 5. After ischaemia/reperfusion the coronary vasoconstrictor responses to B-HT 920 were slightly but significantly enhanced whereas the responses to NA and MTX were unaffected. 6. Thus, in the rat isolated heart, low flow induced-ischaemia and reperfusion causes a selective impairment of muscarinic receptor-mediated vasodilatation but does not impair responses to all endothelium-dependent vasodilators. Enhanced constrictor responses to noradrenaline and B-HT 920 in the presence of Hb indicates that endogenous NO modulates the constriction of coronary resistance vessels in response to stimulation of alpha 2-adrenoceptors. Ischaemia and reperfusion in this isolated vascular bed caused only a small increase in the coronary vasoconstrictor response to alpha 2-adrenoceptor stimulation. It appears that in the rat isolated heart the degree of endothelial dysfunction caused by ischaemia/reperfusion is insufficient to cause a functionally significant change in alpha-adrenoceptor-mediated constriction.

L35 ANSWER 4 OF 20 MEDLINE DUPLICATE 4
AN 96418741 MEDLINE
DN 96418741
TI **Nitric oxide**-donating properties of mesoionic 3-aryl substituted oxatriazole-5-imine derivatives.
AU Kankaanranta H; Rydell E; Petersson A S; Holm P; Moilanen E; Corell T; Karup G; Vuorinen P; Pedersen S B; Wennmalm A; Metsa-Ketela T
CS Medical School, University of Tampere, Finland.
SO BRITISH JOURNAL OF PHARMACOLOGY, (1996 Feb) 117 (3) 401-406. Journal code: B00. ISSN: 0007-1188.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199703
EW 19970304
AB 1. The **nitric oxide** (NO)-releasing properties of two

new mesoionic 3-aryl substituted oxatriazole-5-imine derivatives (GEA
3162
and GEA 3175) were characterized and compared with the known NO-donors
3-morpholino-sydnonimine (SIN-1) and S-nitroso-N-acetylpenicillamine
(SNAP). 2. GEA 3162, GEA 3175, SIN-1 and SNAP inhibited adenosine
5'-diphosphate-induced **platelet** aggregation (IC50 values 0.18,
0.39, 3.73 and 2.12 microM, respectively). All four compounds induced a
dose-dependent and more than 4 fold increase in cyclic GMP in
platelets. The increase in cyclic GMP concentration was
potentiated more than 1.5 fold by a phosphodiesterase inhibitor,
zaprinast
(10 microM) and inhibited 38-97% by oxyhaemoglobin (10-45 microM). 3. All
of the four compounds studied converted oxyhaemoglobin to methaemoglobin
and formed a paramagnetic **NO-haemoglobin** complex. All
but GEA 3175 formed nitrite and nitrate in phosphate buffer. During a 40
min incubation, GEA 3162, SIN-1 and SNAP (100 microM) produced 50-70
microM NO2- + NO3- as determined by high performance liquid
chromatography. The release of NO and NO2 by GEA 3175 was increased 140
fold in the presence of human plasma (0.14 and 19.7 ppb in the absence
and
presence of 1% human plasma, respectively) as analyzed by ozone
chemiluminescence. 4. The results suggest that the mesoionic 3-aryl
substituted oxatriazole-5-imine derivatives GEA 3162 and GEA 3175 as well
as SIN-1 and SNAP release **nitric oxide**.

L35 ANSWER 5 OF 20 MEDLINE DUPLICATE 5
AN 96250486 MEDLINE
DN 96250486
TI Techniques for measurement of **nitric oxide** in
biological systems: principles and practice.
AU Yamamura T
CS International Research Laboratories, Ciba-Geigy, Japan.
SO NIPPON YAKURIGAKU ZASSHI. FOLIA PHARMACOLOGICA JAPONICA, (1996 Apr) 107
(4) 173-82. Ref: 41
Journal code: F2X. ISSN: 0015-5691.
CY Japan
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA Japanese
FS Priority Journals
EM 199610
AB Despite being small and simple in structure the **nitric
oxide** free radical (NO.) is now proving to be of vital
physiological significance, and it has been shown to play important roles
in complex processes such as vasodilatation, inflammation,
thrombosis, immunity and neurotransmission. To conduct meaningful
research into the role of NO., it is necessary to accurately determine
its
concentration. Its direct and quantitative measurement, however, has been
little discussed inspite of the abundance of studies on this compound.
Generally most authors refer to indirect qualitative measurements, such
as
employment of NO-synthase inhibitors, measurement of cGMP or citrulline,
and the detection of NO.-induced physiological effects such as vascular
relaxation. The primary difficulties in the direct measurement of NO stem
from its short lifetime and very low concentrations. Notwithstanding
these
problems, several quantitative methods for measuring NO. have been

established. The most commonly used techniques are as follows: 1) UV-visible spectrophotometry of the diazotization product of the nitrite, **NO-hemoglobin** or methemoglobin, 2) fluorometry of the fluorescent product of the nitrite, 3) detection of chemiluminescence by its reaction with ozone or luminol/H2O2, 4) amperometric microelectrode assay, and 5) electron spin resonance spectrometry. All the aforementioned techniques have certain limitations that should be considered carefully prior to each application.

L35 ANSWER 6 OF 20 MEDLINE DUPLICATE 7
AN 92013133 MEDLINE
DN 92013133
TI Potentiation of tumor necrosis factor-alpha-mediated cytotoxicity of mast cells by their production of **nitric oxide**.
AU Bissonnette E Y; Hogaboam C M; Wallace J L; Befus A D
CS Department of Microbiology and Infectious Diseases, University of Calgary, Alberta, Canada..
SO JOURNAL OF IMMUNOLOGY, (1991 Nov 1) 147 (9) 3060-5.
Journal code: IFB. ISSN: 0022-1767.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English.
FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals
EM 199201
AB **Nitric oxide** (NO or endothelium-derived relaxing factor) has many of biologic actions, including the maintenance of blood pressure, inhibition of **platelet** aggregation, and cytotoxicity by phagocytic cells. Several cell types produce NO from L-arginine. Given recent emphasis on mast cell (MC)-dependent TNF-alpha-mediated cytotoxicity, we investigated the role of NO in rat peritoneal MC (PMC)-and intestinal mucosal mast cell-mediated cytotoxicity. MC cytotoxicity against the TNF alpha-sensitive target, WEHI-164, was potentiated by L-arginine. The NO competitive inhibitors, N omega-nitro-L-arginine and NG-methyl-L-arginine, diminished the cytotoxicity of rat PMC by 27 and 17%, respectively. However, hemoglobin, which binds to NO, inhibited the cytotoxic activity of PMC by 49% in the presence of 1 mM L-arginine and by 24% in L-arginine-free medium. The latter suggests that PMC use intracellular stores of L-arginine to produce **NO**. Neither **hemoglobin** nor NO metabolites affected human rTNF-alpha cytotoxicity. Furthermore, sodium nitroprusside, with its free radical NO group, restored PMC cytotoxicity in L-arginine-free medium to the level observed in 1 mM L-arginine medium. Studies with a **platelet** aggregation bioassay and various NO inhibitors confirmed that PMC produce NO. In addition, increased levels of NO2- were observed in medium of A23187, TNF-alpha, or WEHI-164-stimulated PMC.

L35 ANSWER 7 OF 20 MEDLINE
AN 97053427 MEDLINE
DN 97053427
TI Effects of TNF-alpha on [Ca2+]i and contractility in isolated adult rabbit ventricular myocytes.
AU Goldhaber J I; Kim K H; Natterson P D; Lawrence T; Yang P; Weiss J N
CS Division of Cardiology, School of Medicine, University of California, Los Angeles 90095, USA.
NC RO1 HL-44880 (NHLBI)

SO AMERICAN JOURNAL OF PHYSIOLOGY, (1996 Oct) 271 (4 Pt 2) H1449-55.
Journal code: 3U8. ISSN: 0002-9513.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199702
EW 19970204
AB The mechanism of the acute negative inotropic effect of tumor necrosis factor-alpha (TNF-alpha) was studied in enzymatically isolated adult rabbit ventricular myocytes. In cells loaded with fura 2 acetoxymethyl ester (AM) and paced intermittently at 0.2 Hz, TNF-alpha at doses < or = 10,000 U/ml caused a significant reduction in active cell shortening at 20 min, without reducing the amplitude of the accompanying intracellular Ca2+ concentration ([Ca2+]i) transient. Similar results were obtained in cells loaded with indo 1-AM and paced continuously at 0.2 Hz during exposure to TNF-alpha (10,000 U/ml). The effect of TNF-alpha on cell shortening could be prevented by the **nitric oxide** (NO) synthase blocker NG-nitro-L-arginine methyl ester (L-NAME) but not its inactive enantiomer NG-nitro-D-arginine methyl ester (D-NAME). The **NO** scavenger **hemoglobin** also attenuated the effects of TNF-alpha. TNF-alpha also caused a significant increase in diastolic cell length without any change in diastolic [Ca2+]i. The effect on cell length was prevented by L-NAME but not D-NAME. In cells loaded with the pH indicator seminaphthorhodafluor-AM, TNF-alpha did not alter pH sufficiently to account for the negative inotropic effect. These data suggest that high doses of TNF-alpha can acutely induce NO synthesis in isolated myocytes and reduce contractility by decreasing myofilament [Ca2+]i responsiveness.
The mechanism of this altered myofilament [Ca2+]i response is unknown but does not appear to be pH mediated.

L35 ANSWER 8 OF 20 MEDLINE
AN 95251039 MEDLINE
DN 95251039
TI Sites of inhaled NO-induced vasodilation during hypoxia and U-46619 infusion in isolated lamb lungs.
AU Tod M L; O'Donnel D C; Gordon J B
CS Department of Medicine, University of Maryland School of Medicine, Baltimore 21201, USA.
NC HL-43304 (NHLBI)
SO AMERICAN JOURNAL OF PHYSIOLOGY, (1995 Apr) 268 (4 Pt 2) H1422-7.
Journal code: 3U8. ISSN: 0002-9513.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199508
AB The sites of relaxation in response to inhaled **nitric oxide** (NO) were investigated using the vascular occlusion technique in isolated blood-perfused lungs from 1- to 3-mo-old lambs. In one group of 10 lungs, inhaled NO (45 ppm) was administered during hypoxia- and U-46619-induced pulmonary vasoconstriction. In a second group of 5 lungs, responses to inhaled NO and infused sodium nitroprusside (SNP, 3 micrograms.kg-1.min-1) during U-46619-induced hypertension were

compared. Hypoxia caused significant pulmonary vasoconstriction, with increases in the pressure gradients of large and small arteries and small veins, as defined by vascular occlusion. Inhaled NO significantly reduced the total pulmonary pressure gradient by 67% and relaxed both large and small arteries. Infusion of U-46619 caused significant increases in all segmental pressure gradients. While inhaled NO was effective in relaxing the large and small arteries and the small veins, it had no effect on the large veins. Infusions of SNP, a nitrosovasodilator thought to act like endogenous NO, caused a similar degree of total relaxation as NO (81 vs. 77%, respectively). However, in contrast to inhaled NO, SNP was effective in reducing the pressure gradient of the large pulmonary veins. These results suggest that rapid binding to and thus inactivation of inhaled **NO** by **hemoglobin** limit its efficacy as a pulmonary venous dilator.

L35 ANSWER 9 OF 20 BIOSIS COPYRIGHT 1999 BIOSIS DUPLICATE 6
AN 1994:135155 BIOSIS
DN PREV199497148155
TI Role of **nitric oxide** in eicosanoid synthesis and uterine motility in estrogen-treated rat uteri.
AU Franchi, Ana Maria; Chaud, Marcela; Rettori, Valeria; Suburo, Angela; McCann, Samuel M. (1); Gimeno, Martha
CS (1) Neuropeptide Div., Dep. Physiol., Univ. Texas Southwestern Med. Cent., 5323 Harry Hines Blvd., Dallas, TX 75235-8873 USA
SO Proceedings of the National Academy of Sciences of the United States of America, (1994) Vol. 91, No. 2, pp. 539-543.
ISSN: 0027-8424.
DT Article
LA English
AB Cholinergic stimulation of vascular endothelin activates NO synthase (NOS), leading to generation of NO from arginine. This NO diffuses to the overlying vascular smooth muscle and causes vasodilatation. NOS has also been found in the central and peripheral nervous systems and it is clear now that NO plays an important role as a neurotransmitter. Here we investigate the role of NO in controlling contraction of uterine smooth muscle. Our previous work showed that NO activates the cyclooxygenase enzyme in the hypothalamus, leading to production of prostaglandin E-2 (PGE-2). We began by determining whether NO was involved in production of arachidonic acid metabolites in the uterus. Uteri were removed from female rats that had been treated with estrogen (17-beta-estradiol). Control animals were similarly injected with diluent. Tissues were incubated in vitro in the presence of (14C)arachidonic acid for 60 min. Synthesis of PGs and **thromboxane** B-2 (TXB-2) was markedly stimulated by sodium nitroprusside (NP), the releaser of NO. The effect was greatest on TXB-2; there were no significant differences in increases of different PGs. The response to NP was completely prevented by Hb, a scavenger of NO. The inhibitor of NOS, NG-monomethyl-L-arginine (NMMA), significantly decreased synthesis of PGE-2 but not the other prostanoids (6-keto-PGF-1alpha and PGF-2alpha). Addition of Hb to scavenge the spontaneously released NO inhibited synthesis of 6-keto-PGF-1alpha, PGE-2, and PGF-2alpha, but not TXB-2. There was a much lesser effect on products of lipoxygenase, such that only 5-hydroxy-5,8,11,14-eicosatetraenoic acid (5-HETE) synthesis was increased by NP, an effect that was blocked by Hb; there was no effect of NMMA or Hb on basal production of 5-HETE. Thus, NO stimulates release of the various prostanoids and 5-HETE; blockade of NOS

blocked only PGE-2 release, whereas Hb to scavenge the NO released also blocked synthesis of 6-keto-PFG-1-alpha, PGE-2, and PGF-2alpha, indicating that basal NO release is involved in synthesis of all these PGs, especially PGE-2. Presumably, NMMA did not block NOS completely, whereas Hb completely removed released NO. This may explain the different responses of the various prostanoids to NMMA and Hb. To determine the role of these prostanoids and NO in control of spontaneous in vitro uterine contractility in the estrogen-treated uterus, the effect of blocking NOS with NMMA and of scavenging NO produced by Hb on the time course of spontaneous uterine contractility was studied. Surprisingly, blockade of NOS or removal of **NO** by **Hb** prevented the spontaneous decline in uterine motility that occurs over 40 min of incubation. We interpret this to mean that NO was released in the preparation and activated guanylate cyclase in the smooth muscle, resulting in production of cGMP, which reduces motility and induces relaxation. When the motility had declined to minimal levels, the effect of increased NO provided by NP was evaluated; apparently by stimulating the release of prostanoids, a rapid increase in motility that persisted for 10 min was produced. This effect was completely blocked by Hb. The action of NP was also blocked by indomethacin, indicating that it was acting via release of PGs. Apparently, when motility is low, activation of PG synthesis by NO to activate the cyclooxygenase enzyme causes a rapid induction of contractions, whereas, when motility is declining, NO acts primarily via guanylate cyclase to activate cGMP release; the action of the prostanoids released at this time is in some manner blocked.

L35 ANSWER 10 OF 20 BIOSIS COPYRIGHT 1999 BIOSIS
AN 1984:276932 BIOSIS
DN BA78:13412
TI CYANIDE PREVENTS THE INHIBITION OF **PLATELET** AGGREGATION BY NITROPRUSSIDE HYDROXYLAMINE AND AZIDE.
AU SCHWERIN F T; ROSENSTEIN R; SMITH R P
CS WHITE RIVER JUNCTION, VT 05001, USA.
SO THROMB HAEMOSTASIS, (1983 (RECD 1984)) 50 (4), 780-783. CODEN: THHADQ. ISSN: 0340-6245.
FS BA; OLD
LA English
AB Sodium cyanide (CN-) in concentrations of 10 .mu.M or more prevented the inhibition of epinephrine-(2.5 .mu.M) and of ADP-(4.0 .mu.M) induced primary and secondary aggregation brought about by 10 .mu.M sodium nitroprusside (SNP). Cyanide alone in the same concentration had no effect on **platelet** aggregation induced by epinephrine or ADP. Even when the addition of CN- was delayed for as long as 9 min after epinephrine and SNP, it immediately reversed the SNP block and initiated a bimodal wave of aggregation. The effect of CN- on SNP inhibition of human **platelet** aggregation was apparently competitive and reversible. Although they are less potent inhibitors of **platelet** aggregation than SNP, the effects of hydroxylamine (HA) and azide were also prevented by SNP. Sodium nitrite did not inhibit **platelet** aggregation consistently. The inhibitory effects of glyceryl trinitrate, papaverine and **NO-Hb** on **platelet** aggregation were not prevented by CN-. These interactions probably had no significance in vivo, but indicated that SNP, HA and azide acted on **platelets** and on vascular smooth

muscle by similar or identical biochemical mechanisms. There apparently were at least 2 subclasses of so-called NO vasodilators. The effect of CN- was possible mediated through an inhibition of the formation of NO from SNP, HA and azide.

L35 ANSWER 11 OF 20 DRUGU COPYRIGHT 1999 DERWENT INFORMATION LTD
AN 94-13524 DRUGU P
TI **Platelet** Aggregation, Von Willebrand Factor Antigen and Activity, and Inhaled **Nitric Oxide** (NO) in ARDS Patients.
AU Samama C M; Dreux S; Eyraud D; Bourlier R; Arock M; Lecompte T
LO Paris, F.,
SO Br.J.Anaesth. (72, Suppl. 1, 110, 1994) 1 Tab.
CODEN: BJANAD ISSN: 0007-0912
AV Dpt. Anesth.-Reanim, GH Pitie-Salpetriere, Paris, France.
LA English
DT Journal
FA AB; LA; CT
FS Literature
AN 94-13524 DRUGU P
AB The effect of inhaled **nitric oxide** (NO) on **platelet** aggregation (induced by ADP, collagen, ristocetin) and von Willebrand factor antigen (vWF Ag) and activity (vWF RCO) in 6 patients with ARDS was investigated. No measurable effect was observed in this study. Rapid fixation of **NO** on **Hb** may explain the lack of detectable systemic effect, and, therefore a local antithrombotic effect cannot be excluded. (congress abstract).
ABEX Methods Blood was sampled in the pulmonary and radial arteries immediately before and 1 hr after NO administration (CFPO - 2ppm) in 6 ARDS patients. **Platelet** aggregation was induced by ADP (5 uM), collagen (10 ug/ml), ristocetin (1.5 mg/ml). Results No difference was observed before and after NO administration. In addition, **platelet** aggregation and vWF Ag and activity did not differ between pulmonary and radial artery. (LJ)

L35 ANSWER 12 OF 20 DRUGU COPYRIGHT 1999 DERWENT INFORMATION LTD
AN 95-01400 DRUGU P
TI **Myocardial** relaxant effect of captopril mediated via bradykinin.
AU Anning P B; Grocott Mason R M; Lewis M J; Shah A M
CS Univ.Wales
LO Cardiff, U.K.
SO Circulation (90, No. 4, Pt. 2, I592, 1994) 1 Tab.
CODEN: CIRCAZ ISSN: 0009-7322
AV Department of Pharmacology, University of Wales College of Medicine, Cardiff, Wales.
LA English
DT Journal
FA AB; LA; CT
FS Literature
AN 95-01400 DRUGU P
AB In isolated guinea-pig hearts, bradykinin (BK) caused dose-dependent enhancement of LV relaxation (reduced mono-exponential time constant (TE)) and a transient increase in coronary flow (CF), with no correlation between TE and CF. Captopril (CP) also enhanced LV relaxation, but did not change CF. In the presence of CP, the relaxant effect of BK was

enhanced and the increase in CF prolonged. CP effects were blocked by HOE-140, and BK effects on TE (but not CF) by Hb. BK and CP exert selective **myocardial** relaxant effects, with attenuation by Hb and HOE-140, respectively, suggesting involvement of endogenous BK, B2 receptors and NO. Enhancement of BK effects by CP probably reflects decreased BK breakdown by ACE. Lack of vasodilator activity of CP may reflect the site of BK/NO release. Relaxant actions of CP may be useful in diastolic dysfunction. (conference abstract).

ABEX ACE-inhibitors, e.g. CP, are beneficial in heart failure and LV hypertrophy. ACE increases angiotensin II levels, and inactivates BK which releases **nitric oxide** (NO) from endothelial cells. Exogenous NO enhances LV relaxation. The effects of BK and CP on LV function in isolated ejecting guinea-pig hearts (constant loading and rate; Kreb's buffer; 37 deg) are reported. LV pressure (LVP) was measured using a 2F Millar catheter, and LV relaxation was assessed by a mono-exponential time constant (TE). The effects of BK (0.1-1 nM) alone, CP (1 uM) alone, BK (0.1 nM) after 30 min pretreatment with CP, BK (1 nM) in the presence of the **NO**-scavenger **Hb** (1 uM), and CP in the presence of the B2 receptor antagonist HOE-140 (10 nM) were investigated. BK caused dose-dependent enhancement of LV relaxation (reduced TE by 9% at 0.1 or 1 nM), and a transient (4 min or less) increase in coronary flow (CF) (by 9% at 0.1 nM and by 37% at 1 nM), with no correlation between TE and CF. CP also enhanced LV relaxation (reduced TE by 15%), but did not change CF. In the presence of CP, the relaxant effect of BK (0.1 nM) was enhanced (TE reduced by 16%) and the 9% increase in CF prolonged (by at least 16 min). CP effects were blocked by HOE-140, and BK effects on TE (but not CF) by Hb. (CC)

L35 ANSWER 13 OF 20 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.
AN 1998111981 EMBASE
TI Improved development of in vitro-derived bovine embryos by use of a **nitric oxide** scavenger in a cumulus-granulosa cell coculture system.
AU Lim J.M.; Hansel W.
CS W. Hansel, Dept. of Reproductive Biotechnology, Louisiana State University, Pennington Biomedical Research Ctr., Baton Rouge, LA 70803, United States. hanselw@mhs.pbrc.edu
SO Molecular Reproduction and Development, (1998) 50/1 (45-53).
Refs: 41
ISSN: 1040-452X CODEN: MREDEE
CY United States
DT Journal; Article
FS 021 Developmental Biology and Teratology
LA English
SL English
AB This study was conducted to examine the hypothesis that **nitric oxide** (NO) affects prehatching development of bovine oocytes fertilized in vitro. In experiment 1, inseminated oocytes were cultured in a cumulus-granulosa cell (CG) coculture system to which 0.008 or 0.04 mM of sodium nitroprusside (SNP), a spontaneous NO releaser, was added at 18 to 60 hr postinsemination. Embryo development was greatly (P < 0.001) inhibited by the addition of SNP, regardless of time of addition or SNP concentration. In experiment 2, eight- cell embryos were cultured singly in a defined medium, to which 0.0016, 0.008, or 0.04 mM of SNP was added.

Development to the blastocyst stage was greatly ($P < 0.001$) decreased after addition of SNP compared with no addition. Higher ($P < 0.02$) concentration of NO metabolites was found in developmentally arrested embryos than in developing embryos at 144 hr postinsemination (experiment 3). In experiment 4, blastocyst formation of oocytes cocultured with CGs was significantly ($P < 0.02$) increased after addition of hemoglobin (Hb,
1
.mu.g/ml), an NO scavenger. Prehatching development of oocytes was significantly ($P < 0.05$) increased after addition of Hb at different time intervals (18, 60, or 144 hr postinsemination) in experiment 5. Embryo development was not enhanced by Hb addition to the culture medium in the absence of CGs (experiment 6). Prehatching development of eight-cell embryos derived from a Hb-containing culture system was not promoted by the further addition of Hb after transfer of the embryos to a defined and CG-free single-embryo culture system (experiment 7). In conclusion, NO, which may be secreted from CGs, has an inhibitory role in prehatching development of bovine oocytes fertilized in vitro, and use of an **NO** scavenger, **Hb**, in a coculture system enhances blastocyst formation.

L35 ANSWER 14 OF 20 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.
AN 97250169 EMBASE
TI cAMP induces heme oxygenase-1 gene expression and carbon monoxide production in vascular smooth muscle.
AU Durante W.; Christodoulides N.; Cheng K.; Peyton K.J.; Sunahara R.K.; Schafer A.I.
CS W. Durante, Houston Veterans Affairs Med. Center, Bldg. 109, 2002 Holcombe Blvd., Houston, TX 77030, United States
SO American Journal of Physiology - Heart and Circulatory Physiology, (1997) 273/1 42-1 (H317-H323).
Refs: 41
ISSN: 0363-6135 CODEN: AJPPDI
CY United States
DT Journal
FS 002 Physiology
LA English
SL English
AB Recent studies indicate that vascular smooth muscle cells generate carbon monoxide (CO) via the action of heme oxygenase (HO). Because adenosine 3',5'-cyclic monophosphate (cAMP) is an important intracellular signaling molecule in the regulation of vascular cell function, we examined whether this second messenger modulates the expression of HO and the production of CO by rat aortic smooth muscle cells. Treatment of smooth muscle cells with the membrane-permeable cAMP derivative dibutyryl cAMP or with compounds that increase intracellular cAMP levels (isoproterenol and forskolin) resulted in a concentration- and time-dependent increase in the levels of HO-1 mRNA and protein, whereas the expression of HO-2 remained unchanged. Both actinomycin D and cycloheximide blocked the basal expression of HO-1 mRNA and protein and prevented the cAMP-mediated induction of HO-1. Incubation of **platelets** with cAMP-treated smooth muscle cells resulted in a significant increase in **platelet** cGMP concentration that was partially reversed by treatment of smooth muscle cells with the **nitric oxide** synthase inhibitor N(G)-monomethyl- L-arginine or the HO blocker zinc protoporphyrin-IX. However, the combined addition of these two inhibitors to cAMP-treated smooth muscle cells or the addition of the CO and **NO** scavenger

hemoglobin to **platelets** completely blocked the stimulatory effect on **platelet** cGMP levels. These results demonstrate that cAMP induces the expression of the HO-1 gene and stimulates the formation of CO and NO in vascular smooth muscle cells. The capacity of cAMP to induce the synthesis of guanylate cyclase-stimulatory CO from smooth muscle cells may represent a novel mechanism by which this nucleotide regulates vascular tone.

L35 ANSWER 15 OF 20 JICST-EPlus COPYRIGHT 1999 JST
AN 960884651 JICST-EPlus
TI NO-Chemistry and Biology. Biochemistry of NO. Dynamic Aspects of **Nitric Oxide** Metabolism in Health and Disease.
AU MINAMIYAMA YUKIKO; INOUE MASAYASU
CS Osaka City Univ., Med. Sch.
SO Kikan Kagaku Sosetsu, (1996) no. 30, pp. 143-150. Journal Code: G0298B (Fig. 7, Tbl. 1, Ref. 22)
CY Japan
DT Journal; General Review
LA Japanese
STA New
AB **Nitric oxide**(NO) has been implicated to play critical roles in various physiological processes including the regulation of vascular resistance, **platelet** aggregation, neurotransmission and immune reaction. However, details of the dynamic aspects of NO metabolism remain to be elucidated. The present paper reports the metabolic fate of NO in the circulation and around vascular walls in health and pathologic subjects. To elucidate the fate of NO in the circulation, its adduct, were generated in RBC by NaNO2 and NOC7, NO donors, and the change in cellular levels of **NO**, **NO-hemoglobin** adducts (**NO-Hb**) and nitrite+nitrate in plasma and tissues were determined. Based on the experiments using electron spin resonance(ESR) spectrometer, kinetic aspects of the formation and degradation of **NO-Hb** and its metabolites were described. Significant amounts of **NO-Hb** were generated by incubating RBC with either NaNO2 or NOC7. When injected intravenously to normal rats, **NO-Hb** in NaNO2 and NOC7-treated RBC disappeared from the circulation RBC with a half-life of 30 and 16min, respectively. Intravenous administration of either NaNO2 or NOC7 increased the blood levels of **NO-Hb**. The metabolic fate of **NO-Hb** differ significantly with NaNO2- and NOC7-treated groups both in vivo and in vitro. **NO-Hb** levels in NOC7-injected rats were significantly lower with animals administered GSH than with cotrol group. These results suggested that the metabolic fate of NO might be affected by the thiol status of animals. (author abst.)

L35 ANSWER 16 OF 20 JICST-EPlus COPYRIGHT 1999 JST
AN 930851056 JICST-EPlus
TI **Nitric oxide** and vascular.
AU KOSAKA HIROAKI; SHIGA TAKESHI
CS Osaka Univ., Medical School
SO Kassei Sanso, Furi Rajikaru (Journal of Active Oxygens & Free Radicals), (1993) vol. 4, no. 5, pp. 497-503. Journal Code: L1066A (Fig. 2, Ref. 5) CODEN: KSFREC; ISSN: 0915-8847
CY Japan
DT Journal; General Review
LA Japanese
STA New

AB The physiologic importance of **nitric oxide**(NO), as a vaso-dilator, is rapidly increasing. The NO synthase in the endothelial cells is of constitutive type, but the induction of NO synthase was reported in both vascular endothelial cells and vascular smooth muscle cells. We studied the effect of IL-1 and TNF on NO production in rats, by detecting **NO-hemoglobin** in their blood using electron spin resonance. Either IL-1 or TNF alone stimulated **NO-hemoglobin** formation. Combined administration of IL-1 and TNF markedly enhanced **NO-hemoglobin** generation, demonstrating synergistic character of both stimuli on NO production. Further, LPS and TNF in combination were more potent stimulator of **NO-hemoglobin** production. (author abst.)

L35 ANSWER 17 OF 20 SCISEARCH COPYRIGHT 1999 ISI (R)
AN 1999:48928 SCISEARCH
GA The Genuine Article (R) Number: 153AE
TI **Nitric oxide**-mediated augmentation of polymorphonuclear free radical generation after hypoxia-reoxygenation
AU Sethi S; Singh M P; Dikshit M (Reprint)
CS CENT DRUG RES INST, DIV PHARMACOL, LUCKNOW 226001, UTTAR PRADESH, INDIA (Reprint); CENT DRUG RES INST, DIV PHARMACOL, LUCKNOW 226001, UTTAR PRADESH, INDIA
CYA INDIA
SO BLOOD, (1 JAN 1999) Vol. 93, No. 1, pp. 333-340.
Publisher: W B SAUNDERS CO, INDEPENDENCE SQUARE WEST CURTIS CENTER, STE 300, PHILADELPHIA, PA 19106-3399.
ISSN: 0006-4971.
DT Article; Journal
FS LIFE; CLIN
LA English
REC Reference Count: 41
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB Polymorphonuclear leukocytes (pMNLs), **nitric oxide** (NO), calcium, and free radicals play an important role in hypoxia/ischemia and reoxygenation injury. In the present study, NO donors, sodium nitroprusside (SNP), and diethylamine-NO (DEA-NO) at low concentrations (10 and 100 nmol/L) potentiated, while higher (10 mu mol/L to 10 mmol/L) concentrations inhibited free radical generation response in the rat PMNLs. Free radical generation response was found to be significantly augmented when hypoxic PMNLs were reoxygenated (hypoxia-reoxygenation [H-R]), This increase in free radical generation after reoxygenation or SNP (10 nmol/L) was blocked in the absence of extracellular calcium. SNP (10 nmol/L) or H-R-mediated increases in the free radical generation were prevented by the pretreatment of PMNLs with **NO** scavenger (**hemoglobin**), the polyadenine diphosphate (ADP)ribosylation synthase inhibitor (benzamide) or the calcium channel antagonist (felodipine), A significant augmentation in the nitrite and intracellular calcium levels was observed during hypoxia. Hemoglobin pretreatment also blocked the increase in intracellular calcium levels due to SNP (10 nmol/L) or hypoxia. Thus, increased availability of NO during SNP treatment or H-R, may have led to an ADP-ribosylation-mediated increase in intracellular calcium, thereby increasing the free radical generation from the rat PMNLs. (C) 1999 by The American Society of Hematology.

L35 ANSWER 18 OF 20 SCISEARCH COPYRIGHT 1999 ISI (R)
AN 97:549520 SCISEARCH

GA The Genuine Article (R) Number: XK679
TI cAMP induces heme oxygenase-1 gene expression and carbon monoxide
production in vascular smooth muscle
AU Durante W (Reprint); Christodoulides N; Cheng K; Peyton K J; Sunahara R
K;
Schafer A I
CS VET AFFAIRS MED CTR, 2002 HOLCOMBE BLVD, BLDG 109, RM 116, HOUSTON, TX
77030 (Reprint); BAYLOR COLL MED, DEPT MED, HOUSTON, TX 77030; BAYLOR
COLL
MED, DEPT PHARMACOL, HOUSTON, TX 77030; UNIV TEXAS, SW MED CTR, DEPT
PHARMACOL, DALLAS, TX 75235
CYA USA
SO AMERICAN JOURNAL OF PHYSIOLOGY-HEART AND CIRCULATORY PHYSIOLOGY, (JUL
1997) Vol. 42, No. 1, pp. H317-H323.
Publisher: AMER PHYSIOLOGICAL SOC, 9650 ROCKVILLE PIKE, BETHESDA, MD
20814.
ISSN: 0363-6135.
DT Article; Journal
FS LIFE
LA English
REC Reference Count: 41
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB Recent studies indicate that vascular smooth muscle cells generate
carbon monoxide (GO) via the action of heme oxygenase (HO). Because
adenosine 3',5'-cyclic monophosphate (cAMP) is an important intracellular
signaling molecule in the regulation of vascular cell function, we
examined whether this second messenger modulates the expression of HO and
the production of CO by rat aortic smooth muscle cells. Treatment of
smooth muscle cells with the membrane-permeable cAMP derivative dibutyryl
cAMP or with compounds that increase intracellular cAMP levels
(isoproterenol and forskolin) resulted in a concentration- and
time-dependent increase in the levels of HO-1 mRNA and protein, whereas
the expression of HO-2 remained unchanged. Both actinomycin D and
cycloheximide blocked the basal expression of HO-1 mRNA and protein and
prevented the cAMP-mediated induction of HO-1. Incubation of
platelets with cAMP-treated smooth muscle cells resulted in a
significant increase in **platelet** cGMP concentration that was
partially reversed by treatment of smooth muscle cells with the
nitric oxide synthase inhibitor N-G-monomethyl-L-
arginine or the HO blocker zinc protoporphyrin-IX. However, the combined
addition of these two inhibitors to cAMP-treated smooth muscle cells or
the addition of the CO and **NO** scavenger **hemoglobin** to
platelets completely blocked the stimulatory effect on
platelet cGMP levels. These results demonstrate that cAMP induces
the expression of the HO-1 gene and stimulates the formation of CO and NO
in vascular smooth muscle cells. The capacity of cAMP to induce the
synthesis of guanylate cyclase-stimulatory CO from smooth muscle cells
may
represent a novel mechanism by which this nucleotide regulates vascular
tone.

L35 ANSWER 19 OF 20 SCISEARCH COPYRIGHT 1999 ISI (R)
AN 97:159701 SCISEARCH
GA The Genuine Article (R) Number: WH814
TI **Nitric oxide** attenuates adhesion molecule expression
in human endothelial cells
AU Takahashi M; Ikeda U (Reprint); Masuyama J I; Funayama H; Kano S; Shimada
K
CS JICHI MED SCH, DEPT CARDIOL, MINAMI KAWACHI, TOCHIGI 32904, JAPAN

(Reprint); JICHI MED SCH, DEPT CARDIOL, MINAMI KAWACHI, TOCHIGI 32904, JAPAN; JICHI MED SCH, DEPT CLIN IMMUNOL, MINAMI KAWACHI, TOCHIGI 32904, JAPAN
CYA JAPAN
SO CYTOKINE, (NOV 1996) Vol. 8, No. 11, pp. 817-821.
Publisher: W B SAUNDERS CO, INDEPENDENCE SQUARE WEST CURTIS CENTER, STE 300, PHILADELPHIA, PA 19106-3399.
ISSN: 1043-4666.
DT Article; Journal
FS LIFE
LA English
REC Reference Count: 22
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB Leukocyte adhesion to vascular endothelium is a crucial step in the early stages of atherosclerosis, which may be mediated by the interaction of adhesion molecules expressed on the surfaces of both cell types. in this study, we investigated the effects of **nitric oxide** OVO) on the expression of intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) in human umbilical vein endothelial cells (HUVECs). ICAM-1 and VCAM-1 protein and mRNA expression were determined by cellular ELISA and Northern blot analysis, respectively. Both ICAM-1 and VCAM-1 expression were increased markedly by interleukin-1 beta(IL-1 beta). This IL-1 beta-mediated induction of ICAM-1 and VCAM-1 expression was significantly inhibited in the presence of a NO donor 3-morpholino-sydnonimine (SIN-1) in a dose-dependent manner. The inhibitory effect of SIN-1 was abolished in the presence of a **NO** scavenger **haemoglobin**, while addition of 8-bromo-cGMP showed no significant effect on IL-1 beta-induced ICAM-1 or VCAM-1 expression. Northern blot analysis showed that IL-1 beta markedly increased ICAM-1 and VCAM-1 mRNA expression, while SIN-1 decreased the accumulation of these transcripts induced by IL-1 beta. These results suggest that NO could prevent the focal adhesion and accumulation of leukocytes through the inhibition of ICAM-1 and VCAM-1 expression in endothelial cells. (C) 1996 Academic Press Limited.

L35 ANSWER 20 OF 20 SCISEARCH COPYRIGHT 1999 ISI (R)
AN 96:109961 SCISEARCH
GA The Genuine Article (R) Number: TR497
TI INHIBITION OF **NITRIC-OXIDE** FORMATION WITH L-CANAVANINE ATTENUATES ENDOTOXIN-INDUCED VASCULAR HYPOREACTIVITY IN THE RAT
AU CAI M (Reprint); SAKAMOTO A; OGAWA R
CS NIPPON MED COLL, DEPT ANAESTHESIOL, BUNKYO KU, 1-1-5 SENDAGI, TOKYO 113, JAPAN (Reprint)
CYA JAPAN
SO EUROPEAN JOURNAL OF PHARMACOLOGY, (11 JAN 1996) Vol. 295, No. 2-3, pp. 215-220.
ISSN: 0014-2999.
DT Article; Journal
FS LIFE
LA ENGLISH
REC Reference Count: 23
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB L-Canavanine, a selective inhibitor of inducible **nitric oxide** (NO) synthase, has beneficial effects on the circulatory failure of rats with endotoxin shock. To investigate the direct relationship between these beneficial effects and the inhibition of the

formation of NO in response to L-canavanine in endotoxin shock in the rat,
we detected changes in venous nitrosyl-hemoglobin (**NO-hemoglobin**) levels using an electron spin resonance (ESR) assay. Anaesthetized rats were injected with lipopolysaccharide (10 mg/kg i.v.). 1 h after the lipopolysaccharide injection, the rats were divided into four groups: a lipopolysaccharide group receiving 0.3 ml of saline hourly,
an L-canavanine 10 or an L-canavanine 20 group receiving L-canavanine 10 or 20 mg/kg i.v. hourly, respectively, and an L-NAME group receiving N-G-nitro-L-arginine methyl ester (L-NAME) 15 mg/kg followed by 10 mg/kg i.v. hourly. A sham group received saline instead of lipopolysaccharide, and an L-canavanine group received L-canavanine 20 mg/kg i.v. hourly, 1 h after the saline injection. At 5 h after the lipopolysaccharide or saline injection, presser responses to noradrenaline (1 mu g/kg i.v.) were obtained. In the lipopolysaccharide group, lipopolysaccharide caused a progressive decrease in mean arterial pressure and an impairment of presser responsiveness to noradrenaline. Administration of L-canavanine or
L-NAME attenuated the endotoxin-induced hypotension and vascular hyporeactivity to noradrenaline. L-Canavanine did not alter mean arterial pressure and the presser response to noradrenaline in the L-canavanine group. The endotoxin-induced increases in venous levels of **NO-hemoglobin** were significantly inhibited by L-canavanine or L-NAME. These data indicate that the beneficial hemodynamic effects of L-canavanine are associated with inhibition of the enhanced formation of NO by inducible NO synthase in a rat model of endotoxin shock. L-Canavanine is a potential agent in the treatment of endotoxin shock.